PROCEEDINGS

ST VINCENT'S CLINIC, SYDNEY

VOLUME 13 No:1 SEPTEMBER 2005

INSIDE THIS ISSUE ...

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PROCEEDINGS

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EDITORIAL

Dr John O'Neill MD, FRACP

Consultant Neurologist

Editor, Proceedings

St Vincent's Clinic has just celebrated its 15th anniversary. It is therefore fitting that this, the 17th Issue of Proceedings, is the largest to date. As usual it contains a mix of clinical and research work covering medical and surgical topics of contemporary interest.

The 11th Sandra David Memorial Lecture examines areas of stem cell research on St Vincent's Campus. Professor Bruce Brew writes on the potential benefits of stem cell research in the treatment of Neurodegenerative disorders such as Alzheimer's disease. Dr Jason Kovacic looks at the potential for cardiac stem cells to revascularise ischaemic myocardium, thereby improving symptoms in patients with untreatable angina. Dr Oleskevich explores the use of adult olfactory stem cells to reverse or slow hearing loss. Dr Bernadette Tobin discusses the ethical issues associated with this type of research.

Dr Chris Bradbury, Consultant Gynaecologist, provides a short treatise on hysterectomy, noting its increased demand in the treatment of benign gynaecological pathologies over recent years. He addresses the issue of choice now available to women and he highlights the importance of informed consent between the doctor and patient.

The article by Doctors Peter Vale and Michael McGrath, Vascular Physicians, is a comprehensive review of the presentation, diagnosis and treatment of patients with peripheral arterial disease. The article highlights the increasing use of stenting as an alternative to surgery when interventional therapy is required.

Dr John Sheehy, Senior Neurosurgeon, is an expert in skull base surgery. In his article he identifies when minimal or maximal surgical exposure is likely to be the ideal approach for removal of various skull base tumours.

The management of certain malignant tumours has recently been advanced by the use of molecular genetics to identify which patients are more likely to respond to chemotherapy. Dr Adrienne Morey, Anatomical Pathologist, describes the new technique of Fluorescent In Situ Hybridisation (FISH) and its application, in particular, to breast cancer and certain primary malignant brain tumours (anaplastic Oligodendrogliomas).

Cataract is one of the four major causes of visual morbidity in Australia. By age 80, 80% of the population will have evidence of cataract. Dr John Kennedy, Ophthalmologist, reviews the evolution of cataract surgery, emphasising modern treatment.

Health Assessment Clinics were relatively novel in Australia when Dr Peter O'Brien established the St Vincent's Health Assessment Clinic in 1991. This is now a highly regarded institution for both corporate and private clientele seeking to cover health and lifestyle risk and detect early disease. Professor Ronald Penny and Dr Peter Slezak review the concept of health risk assessment and the involvement of a private company, Good Health Solutions, which acquired the St Vincent's Health Assessment Centres (Sydney and Melbourne) from 2003.

The article by Dr Reginald Lord, Upper Gastrointestinal Surgeon, provides a comprehensive review of the presentation, diagnosis and medical and surgical treatment of the common condition of gastroesophageal reflux.

Lastly, Doctors Champion and Lee provide a scholarly review on hyperuricaemia not just with respect to its obvious implication in gout but emphasising the increasingly recognised relationship with hypertension, cardiovascular and renal disease.

Page 41 of the Issue lists the Research Grants which have been funded by the St Vincent's Clinic Foundation in 2005. These total $330,000, the major grant being the Ladies Committee Sister Mary Bernice Grant ($100,000) recognising the great work of fundraising undertaken each year by the Ladies Committee of St Vincent's Private Hospital. It should be noted that the aforementioned stem cell research (Sandra David Oration) on St Vincent's Campus has been funded by Grants from the St Vincent's Clinic Foundation of at least $1 million over three years from 2004.

THE SANDRA DAVID ORATION
ST VINCENT'S CAMPUS ADULT STEM-CELL RESEARCH

Adult Stem-Cell Based Therapies for Neurodegenerative Disorders

Professor Bruce James Brew
MBBS MD FRACP
Department of Neurology
St Vincent's Hospital

Currently, there is little in the way of effective treatment for neurodegenerative disorders in general. These include diseases such as Alzheimer's disease and most other dementias, motor neuron disease, multiple sclerosis, and so on. Moreover, even when effective therapies become available there will be still be a large number of patients with fixed neurological damage that reflects the particular disease before the availability of the new therapy.

An alternative approach to helping such patients is to tackle the problem "at the other end" so to speak. In other words, to try to replace the diseased tissue either as an ongoing process when there is no effective primary treatment for the disease, or as a means of repairing/replacing damaged tissue when there is effective treatment. A way of replacing/repairing damaged nervous tissue is through the use of stem cells. A common objection to this strategy is that surely the patient's own cells have already tried to do this and failed. This may be so – the patient's own supply of stem cells may have become exhausted or there may be a "block" to either recruiting or differentiating the patient's own stem cells. Nonetheless, transplantation of stem cells could still be useful even if one or both processes were operative: they could be given in large enough numbers to overcome the dearth or the "block".

As is now commonly known there are several sources of stem cells: embryos and adult tissues. Embryonic stem cells are currently popular in the scientific community because of their ability to differentiate into a variety of cells including those of the central nervous system. There are, however, significant problems with the use of such cells, both ethically and scientifically. The use of discarded embryos as a source for stem cells is ethically unacceptable to most. Scientifically, there is the concern that a proportion of such cells when transplanted will become malignant and there are still concerns over the possibility of such transplanted tissue being immunologically rejected despite recent advances to render such cells immunologically recognizable as "self".

Stem cells from adult tissues on the other hand do not pose any of these problems; malignant transformation has only recently been reported but this occurred after the cells had been cultured in the laboratory for an unduly long period. Virtually any adult tissue has a resident population of stem cells, even the brain. However, the stem cells derived from the bone marrow are generally considered the best source of such cells for a variety of reasons. First, they can be obtained relatively easily by a bone marrow aspirate – a commonly performed procedure requiring only local anaesthetic. This is in contrast to stem cells that are resident in the brain, the so-called neural stem cells. These reside only in particular areas of the brain that are not readily accessible short of operative intervention. Second, the number of stem cells obtained from the bone marrow is relatively high and can be expanded in culture without loss of their multilineage potential.

The stem cells derived from the bone marrow are termed mesenchymal stem cells or marrow stromal cells (MSCs). Curiously, these cells were described for the first time in 1968 but their importance went unrecognized for years. MSCs can be separated from hematopoietic cells by their plastic adherence properties but more precise methodologies are awaited: no specific marker has been described so far. Thus a negative selection process is required – they do not express cell markers of hematopoietic lineages such as CD34, CD45, CD11 or CD14.

How good is the evidence that MSCs can generate cells of different lineages especially those of the nervous system? The data is convincing for transplanted MSCs generating osteoblasts, adipocytes, chondrocytes, myoblasts, and early progenitors of neural cells. It remains controversial as to whether MSCs can differentiate into all the cells of the nervous system, especially those with highly specialized functions such as the cells of the basal ganglia. The evidence is still controversial for MSCs differentiating into oligodendrocytes, the white matter forming cells of the brain.

To address this issue my research group has collaborated with Professor David Ma and his group on this campus as well as with Professor Darwin Prockop in New Orleans. Dr Juliana Lamoury, the senior scientist in my research group, used MSCs in an animal model of multiple sclerosis, the twitcher mouse. This model has been primarily used to study another degenerative disorder, Krabbe's disease. Nonetheless, it is quite a good model for the study of multiple sclerosis as affected mice are normal at birth, but by 20 days of age show signs of tremor and then progress to paralysis followed by death at approximately 40 days. The pathological basis of this degeneration is the accumulation of a toxic metabolite in oligodendrocytes which then leads to the degeneration of myelin. Using labelled human MSCs we transplanted the cells into both neonatal and adult mice through direct

THE SANDRA DAVID ORATION
ST VINCENT'S CAMPUS ADULT STEM-CELL RESEARCH

implantation of the cells into the brain while the mice were under anaesthetic. The control group underwent a sham operation under anaesthetic. The adult mice had to be treated with an immunosuppressant medication, cyclosporine, to prevent rejection of the transplanted MSCs. When a mouse reached a moribund condition, characterized by the animal's inability to perform voluntary movement and severe wasting, it was killed by an overdose of anaesthetic. The mice were then subjected to an autopsy where brain tissue was taken and further studied by light microscopy and immunohistochemistry for markers to identify various brain cells. The transplanted cells could be seen to have migrated through the brain to varying extents. Despite this migration there was no disruption to the brain tissue. Moreover, from co-localization studies it was evident that some of the cells had differentiated into astrocytes, neurons and oligodendrocytes, at least by the expression of cell surface markers (Figure 1). The transplanted mice did not display any clinical benefit. This is most likely related to the small number of MSCs that were transplanted, because only a minority of these were seen to differentiate into intrinsic brain cells.

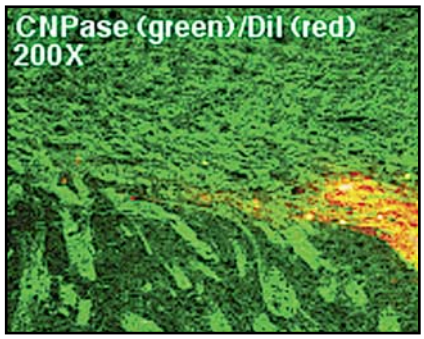

Figure 1: *Section of brain showing white matter stained green with CNPase and transplanted MSCs labelled red. Note the brown -yellow areas signifying probable differentiation into oligodendrocytes.*

We intend to obtain highly purified MSCs from human bone marrow that have the greatest potential to subsequently differentiate along neural lineages. To this end we have already identified a subpopulation of MSCs that seem to be preferentially neurally fated. Further work to more accurately identify this population is, however, needed. Moreover, it is critically important to use this subpopulation for transplantation and to monitor the mice closely for functional improvement.

A Stem-Cell Based Approach to Coronary Artery Disease

Jason C. Kovacic and Robert M. Graham on behalf of the Victor Chang Cardiac Research Institute and St Vincent's Hospital Cardiac Stem-Cell Group*

Coronary artery disease and subsequent myocardial ischaemia represents one of the greatest disease burdens in the Western-world. Given the current ageing of the population and disease trends, chronic myocardial ischaemia and resultant heart failure are predicted to increase dramatically in prevalence over the following decades. Although recent advances have helped to ameliorate myocardial ischaemia and failure, definitive therapies for these disorders are urgently required.

Over the past decade, animal studies have given great insights into the fact that cardiac stem cells, and even stem cells from outside the heart, might be able to repair damaged hearts. It is now accepted that the adult heart contains specialised "cardiac stem cells" which live amongst the heart muscle cells. These cardiac stem cells seem to be capable of forming new heart muscle cells and other tissues of the heart (like blood vessels). However, we do not yet understand why these stem cells are unable to fully repair a damaged adult human heart (for example, after a heart attack). Although somewhat controversial, several studies have now also demonstrated that bone marrow stem cells might be able to change into cardiac cells and help to repair the damaged heart.

On the basis of this impressive body of animal research, and given the urgent need to alleviate the burden of cardiac disease faced by society, a combined team from the Victor Chang Cardiac Research Institute and St Vincent's Hospital (SVH) recently initiated an ambitious clinical trial to test the use of stem cells to help patients with a poor blood supply to the heart. Design of the trial began in 2002, and involved a multi-disciplinary team including representation from cardiology, haematology, nuclear-medicine, and cardiac basic science. In order to ensure that the trial is executed in a rigorous and objective manner, an independent data and safety monitoring board was also established (an initiative seen in a positive light by the SVH Human Research Ethics Committee).

The trial aims to recruit 20 patients with severe coronary artery disease, who suffer from frequent angina (chest pain), and who cannot be helped by further medications, coronary bypass graft surgery or coronary artery stenting. So far, 11 patients have been enrolled into the trial. The design of the trial borrows from well-established haematological methods, which are used to obtain stem cells from the bone marrow and then perform a bone marrow stem cell

THE SANDRA DAVID ORATION
ST VINCENT'S CAMPUS ADULT STEM-CELL RESEARCH

transplant (done routinely at SVH for many years). Thus, a special drug that stimulates bone marrow stem cells to multiply and enter the circulation (called "G-CSF") is given to the trial patients for 5 days. After this time specific stem cells that are capable of forming new blood vessels can be detected in the blood stream. Then, using a series of carefully administered graded exercise sessions and the induction of controlled angina in the patients, the stem cells are encouraged to migrate into the heart and form new blood vessels in the areas of the heart with a poor blood supply. After 3 months this entire process (5 days of G-CSF and graded exercise sessions) is repeated again, but on this second occasion some of the stem cells are collected from the blood stream, and then directly injected into the heart arteries in the catheterisation laboratory.

Six patients have now completed the trial. Despite the very poor prognosis of these patients, all remained alive and well during and subsequent to the trial. We have been greatly encouraged by their initial reports of improvements in their symptoms, and in particular the reduction in the amount of angina they experience. However, we are being extremely careful to not over-interpret these highly-subjective and preliminary observations. We await the proper conclusion of the trial and a formal analysis of our data before drawing any firm conclusions about the success, or otherwise, of this new therapy.

It is anticipated that the trial will run for a further 18 months, with final results being available soon thereafter. Given that the trial is being carefully controlled and executed, it is likely that it will generate widespread interest from a worldwide audience.

Other members of the group include: Prof. D. Ma, Prof. M. Feneley, A/Prof P. Macdonald, A/Prof D. Muller, A/Prof J. Freund, and Drs. A. Dodds, J. Moore, S. Milliken, J. Freund, H. Tao, and Ms. A. Herbert, as well as our collaborator A/Prof. S. Itescu, Cornell University, New York.

Using Adult Stem-Cells for the Treatment of Hearing Loss

Dr Sharon Oleskevich PhD, on behalf of the Hearing Research and Neural Stem-Cell Group*, Garvan Institute of Medical Research, and St Vincent's Hospital ENT Department

Hearing loss is a debilitating disease that affects a significant proportion of the population worldwide. In particular, one in five Australians over the age of 15 (3 million people) suffer some degree of hearing loss. As our population continues to live longer, the proportion of people affected by age-related hearing loss will increase. The growth of industrialised countries will also increase the number of people affected by noise-induced hearing loss. The overall aim of our research project is to use stem cells as a treatment for the reversal or slowing of hearing loss in humans.

Of the five senses, hearing is the most finely tuned sense, capable of detecting sounds over a thousand-fold range. Hearing is also the most fragile sense. The hearing cells (hair cells) are vulnerable and degenerate with ageing, following excessive sustained noise, certain antibiotic treatments and infection. High-frequency sounds such as speech consonants are commonly missed, and word recognition becomes difficult especially in situations of loud background noise. Hearing loss can result in eventual breakdown of communication skills and social isolation. The only treatment at present addresses the symptoms with prostheses such as hearing aids or cochlear implants, and fails to prevent the process of disease progression. The hair cells are not replaced in humans, thus the sensory deprivation is permanent and irreversible.

In the last decade, extensive efforts have been directed towards using stem cells to generate new hair cells to replace those lost in deafness. Research groups have successfully transformed stem cells into hair cells, first in a culture dish and then in the inner ear of laboratory animals. Despite positive results in animal studies, it has not been established whether the new hair cells make the appropriate connections to the brain and thus restore hearing. A new research program was initiated at the Garvan Institute to combine stem cell research with hearing research. We extend previous findings by using a novel source of stem cells and by applying new techniques to test for appropriate connections of hair cells to the brain.

Adult olfactory stem cells from the nasal lining were chosen as the source of stem cells. Adult stem cells possess multiple advantages over embryonic stem cells in that they avoid ethical embryonic issues, tumour growth, tissue rejection, and the need for additional neuronal differentiation steps. The nasal lining is replaced every 60 days and thus provides an abundant and easily accessible source of autologous stem cells. Differentiation of olfactory stem cells into hair cells has not been previously reported and represents a highly innovative approach. Over the past 2 years, we have developed methodology to isolate the nasal lining of mice and grow the stem cells in a culture dish. Our experiments show that adult mouse olfactory stem cells possess

THE SANDRA DAVID ORATION
ST VINCENT'S CAMPUS ADULT STEM-CELL RESEARCH

two hallmarks of classical stem cells, that is they are self-renewing (can make multiple copies of themselves) and multipotent (can transform into a variety of cell types). We are currently employing a variety of techniques to transform the stem cells into hair cells in a culture dish. Recent results show that stem cells can be successfully transformed into hair cells when they are exposed to a solution derived from the mouse cochlea (inner ear; see Figure 1).

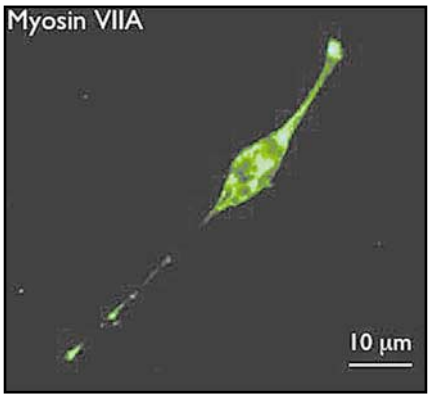

Figure 1. *New hearing/hair cell generated from an adult stem cell in culture.*

The cell is labelled with Myosin VIIA, a specific marker for hair cells.

Our long-term goal is to transfer our research from bench to bedside, in an effort to treat the debilitating disorder of hearing loss. The project uniquely brings together expertise in molecular biology, stem cell biology and electrophysiology, together with the clinical expertise of internationally recognized ear surgeons situated on campus at St. Vincent's Hospital. We expect the animal studies to begin within two years and, if successful, a progression to human studies will follow. We thank the generous support of St Vincent's Clinic Foundation and additional support from the Fairfax Foundation and BHP Billiton Community Fund.

*Other members of the Hearing Research and Stem Cell Group include Prof J. Shine, Dr K. Doyle, Dr S. McKay and Ms Y. Hort and our collaborators at St. Vincent's Hospital, Dr J. Tonkin and Dr T. Corlette.

Stem-Cells: Some Ethical Issues

Bernadette Tobin, PhD
Plunkett Centre for Ethics
St Vincent's Hospital

Technologies based on stem cells offer wonderful possibilities for the restoration of human health. Not only do these technologies have the potential to repair damaged and impaired tissues and organs: they also have the potential, it seems, to regenerate tissues and organs and thus to restore proper bodily functioning in someone whose body has been injured, disabled or diseased. In thinking about the ethical issues associated with the development and use of these technologies, the place to start is, I think, in recognition of the extraordinariness of the new knowledge we are acquiring, knowledge of how the human body works and of the capacities it contains within itself to restore its own proper functioning. No wonder scientists are so excited about this knowledge: for quite apart from its therapeutic potential, the pursuit of new knowledge in itself is genuine human good. Indeed, Aristotle thought that the desire to know and understand the world, even when knowledge held out no practical advantage for the knower, is what sets human beings apart from other animals!

So, let us start by acknowledging not only the good of developing therapies to relieve illness, disease and deformity but also the good of pursuing knowledge in and of itself. These goods are truly worthy human objectives or 'ends'. But, as we know, in human affairs the end sought does not justify the means employed. Any ethical evaluation of stem cell technologies must address the means used in the pursuit of these ends. The ethical requirement to do so ought not to be side-stepped by, for example, so inflating the value and the likelihood of the achievement of their therapeutic potential that the pursuit of that goal is made to seem overwhelmingly desirable or (even worse) obligatory!

The most controversial of the means employed in the pursuit of knowledge about how stem cell technologies may help us to understand health and disease and to develop healing therapies is that of the destruction of human embryos. (This is likely soon to be accompanied by the creation of embryos solely for the purpose of use in research which will involve their destruction.) Here the question to be addressed is that of the status of the human embryo, whether it is properly to be thought of as belonging to what philosophers call a 'natural kind' every member of which (however embryonic or aged, able or disabled, wanted or unwanted, etc) deserves that sort of unconditional respect which prohibits deliberate killing, or whether it is properly to be thought of as an entity which does not (yet) qualify for the sort of unconditional respect which prohibits deliberate killing because it does not (yet) possess the characteristic of self-consciousness which is a necessary feature of beings who deserve such respect.

Men and women of goodwill can and do differ in their thinking about the status of the human embryo. The position endorsed in the Catholic tradition is a cautious one: since the question involves deep and difficult metaphysical problems, the human embryo ought to be given the benefit of the doubt and treated as though it were the kind of being worthy of the sort of unconditional respect incompatible with its deliberate killing. And so, the *Code of*

THE SANDRA DAVID ORATION
ST VINCENT'S CAMPUS ADULT STEM-CELL RESEARCH

Ethical Standards for Catholic Health and Aged Care Services in Australia limits research on human embryos in Catholic institutions to that in which there is a moral certainty of causing no harm to the life or integrity of the embryo. No Catholic research institution may produce, damage or dismember a human embryo to remove stem cells.

Let us, therefore, set aside further consideration about the ethics of research which involves the destruction of human embryos. For according to the thinking found in our Catholic tradition, human embryos are members of the 'kind' of being to which common morality's prohibition on the killing of the innocent applies. If so, then no amount of talking up the therapeutic potential of embryonic stem cells (a cure for quadriplegia, for Alzheimer's, for Parkinson's), accompanied by talking down the therapeutic potential of non-embryonic stem cells ('they are too hard to find', 'there aren't enough of them', 'they don't sufficiently proliferate', ...) should make any difference. If the means chosen to some undeniably good end is *itself* unethical, then enough said. (Of course, this view of common morality's negative prohibitions, that they apply absolutely, is denied by the currently-fashionable consequentialist school of philosophy which teaches that all that matters are the consequences (or 'outcomes') of our choices: but that is another story.)

However, as we all know, the human embryo is only one of several sources of stem cells. The umbilical cord is second source. And a third is the adult human body itself: most of our tissues and organs seem to contain so-called 'adult' stem cells. Tonight we have heard of research on cardiac stem cells which is aimed at exploring their potential therapeutic use in coronary artery disease, research on olfactory stem cells which is aimed at hearing repair, and research on neural stem cells which is aimed at the relief of neurodegenerative disorders. Once again, the very great desirability of the goals sought in research on 'adult' stem cells ought not to blind us to its ethical challenges. Let me mention just a few which were recently outlined with respect to using neural stem cells to repair spinal cord injuries. Spinal cord injury is an area of medicine which so far has been limited largely to providing supportive care to prevent a bad situation from becoming worse. Now stem cell technologies in neural surgery and cellular transplantation for spinal cord injury hold out the extraordinary possibility of actually repairing damaged tissues. The ethical challenges are both serious and representative of the ethical challenges throughout the field of stem cell research. I shall mention three such challenges, ones which were recently identified by two neurosurgeons (Drs Rosenfeld and Gillett) writing in the *Medical Journal of Australia*.[1]

There are ethical issues associated with the selection of patients. Because of the plasticity of repair in the young, neural transplants into the spinal cords of the young may produce better results than if the host is an adult. In addition, the return of spinal cord reflex activity below the level of experimental lesion would need to be distinguished from that of recovery of complex coordination and balance lost through injury. And due recognition needs to be given to the fact that the less neurologically impaired the patient, the greater the likelihood that manipulation of the spine will produce a worsening of function. And, again, the ethical issue of subjecting paraplegic and quadriplegic patients to sham spinal surgery for the purpose of controlled comparisons, in order to clarify the difference between genuine and placebo outcomes, will have to be faced.

There are ethical issues associated with the long-term risks to patients. For example, genetically engineered stem cells may harbour oncogenes (which could theoretically induce late tumours in the graft of stem cells).

And there are ethical issues associated with the pressure to apply stem cell techniques. Pressure from patients, biotechnology companies and universities can diminish scientific patience and objectivity. Neural repair is increasingly being recognized as a prolonged process, for which it may be necessary to wait months or years for any clear indication of benefit. And so the desire to apply stem cell techniques, whether to advance one's professional career or simply to help suffering patients, may dilute our 50-year-old ethical standards about research merit and safety: for example, that a research proposal must be justifiable in terms of its potential contribution to knowledge, must be based on a thorough study of current literature as well as on prior observation, previous studies and relevant laboratory and animal studies, and must be designed to ensure that any risk of discomfort or harm is balanced by the likely benefits to be gained by the participants.

Rosenfeld and Gillett conclude, rightly in my view, that the wonderful therapeutic potential of stem cell technologies 'almost silences' the sternest critics of these technologies: for the technologies offer new scope for healing human beings with intelligence, creativity and compassion. But they are frank about the seriousness of the ethical challenges associated with the use of 'adult' stem cells. As they say, how these challenges are faced will reflect, and (I would add) influence, the ethics of the medical profession. And perhaps the greatest challenge of all for doctors will be to do their part to ensure that the therapeutic benefits are available to all in need. The expense involved in tailoring the technologies to the individual patient, together with the increasing penetration of market arrangements into the funding of, and access to, health care, may make justice in the distribution of the benefits of health care even harder to achieve.

1 Jeffrey V Rosenfeld and Grant R Gillett: Ethics, stem cells and spinal cord repair', *Medical Journal of Australia*, Vol 180, 21 June 2004, pp 637-8

Dr Christopher Bradbury

Hysterectomy – 100 years of choice

Introduction

A surgical management that best illustrates choice is hysterectomy for benign gynaecological pathology.

During Plato's time, it was said that the 'hyster' (the uterus) was an "animal endowed with spontaneous sensation and motion, lodged in a woman ardently desiring to produce children. If it remains sterile long after puberty it became indignant, dissatisfied and ill tempered and caused general disturbance of the body until it became pregnant, when it returned to normal again."

Hysteria in Hippocrates time was due to an abnormal uterus. If only it could be excised – hysterectomy.

History

In 1822, Sauter recorded the first abdominal hysterectomy with disastrous outcome. This operation was not popularly thought of for the next seventy years.

In the 1890s Wertheim rekindled the operation.

In 1905, Dame Constance D'Arcy was appointed to the Royal Hospital for Women, Paddington and soon after St Vincent's Hospital, Darlinghurst. Hysterectomy in Sydney began in earnest again but with significant complication rates. This was an era of little choice for women.

Incidence

In the 1950s, less than 5% of the female population aged 40-55 underwent hysterectomy. Now up to 20% of the female population aged 40-55 have hysterectomy performed. Hysterectomy rates in Western society vary from 3 to 3.5 per 1000 total population in Australia and the UK to Canada and the USA where rates of 6.3-6.9 per 1,000 are the accepted norm.

In 1999, the National Health Priorities and Quality Branch of Commonwealth Department of Health and Aged Care in Australia, looked at data from New South Wales, ACT and Queensland and found three major indicators for hysterectomies that were higher than expected.

- Disorders of menstruation
- 20-44 age group
- Low socio-economic group

The Demand for Hysterectomy

There is little doubt there has been an increasing demand for hysterectomy, especially over the last 30 years and it is not unreasonable to expect that high levels of satisfaction will encourage the clinician and patient alike to adopt a positive outlook towards the operation. This demand is continuing to rise, with good outcomes and low complication rates.

Is this attitude justified?

The best available data to answer this question is available in a very large UK Prospective Study published in 2004 by McPherson, Metcalf et al at the Nuffield Department of O & G in collaboration with significant others including the Royal College of Obstetricians and Gynaecologists and the Medical Research Council with the Medical Research Council Clinical Trials Unit in London. This collaboration performed a twelve month survey involving 350 hospitals in England, Wales and Northern Ireland and looked at major operative and post operative complications associated with hysterectomy for benign causes.

Review of the Evidence

There were 37,295 procedures performed, and the average age of the women in the review was 45.

The breakdown of indications in this English study were identical to our Australian experience.

- Dysfunctional uterine bleeding - 46%
- Fibroids - 19%
- Prolapse - 19%
- Endometriosis / Adenomyosis - 6%
- Other - 10%

The type of procedure performed was two thirds abdominal hysterectomy and one third vaginal hysterectomy, as expected. There were only a small number of laparoscopic assisted procedures as the survey was completed before significant development in these techniques. Only 5% laparoscopic procedures were recorded.

The death rate was found to be a total of 14 deaths in 37, 295 procedures, that is 0.38 per 1,000.

There were no recorded deaths during surgery. There were 3.5% major operative complications and 1% major post operative complications. There were no differences between abdominal or vaginal rates of major complications.

It is important to understand that this study looked at major complication rates. It has been consistently shown that minor complication rates are lower with the vaginal method of surgery. Good studies showing this come from Australia, UK and the USA.

Christopher Bradbury MBBS, FRCOG, FRANZCOG
Gynaecologist
St Vincent's Clinic

This UK study has been the biggest prospective multicentred look into the risks of hysterectomy for benign pathology and concludes that this method of management has a relatively low death and major complication rate and therefore justifies the important place of the operation in the management of uterine related women's health.

Is it possible to identify more major risk in the surgery and as a result minimise further this major complication concern?

Major Risk Factors for Hysterectomy

Increasing size of uterus and fibroids and other associated pathology greatly increase surgical risks, especially in the younger patient. This reflects the effect of anatomical distortion and pelvic vasculature in surgical pelvic dissection. The factors that will reduce major complication rates in hysterectomy surgery are:

- Early intervention in pelvic pathology
- Meticulous surgical technique (surgical training)
- Careful selection of appropriate method of surgery and surgeon
- Best practice principles to reduce incidence of sepsis

Laparoscopic Approach

Laparoscopic methods of surgery are gaining in incidence and clearly patients are beginning to ask for this method of surgery. Up to date there has been a significantly higher incidence of bladder and ureteric complications with laparoscopic procedures overall. Where surgical skills have been allowed to develop and improve in many units throughout Australia, there is no demonstrable difference in major complication rates compared with vaginal or abdominal procedures. Laparoscopic figures will continue to improve with improving technique, skills, instrumentation and surgical temperament.

The major determinant as to whether a surgical management is utilised will be a patient exercising her choice.

How do Patients Choose?

J. M. Young and M. Solomon in an excellent article published in the ANZ Journal of Surgery in 2003, described evidence based patient choice in surgery. They outlined three elements in decision making for a patient when faced with surgery as a method of their management. These were:

- Evidence based medicine
- Patient involvement in choice
- Cost effectiveness analysis in surgery

It is clear that management decisions in surgery have moved from doctor pronouncement of yesteryear to patient request and choice of today. There has been no sub-speciality of surgery where this is more evident than in women's health with caesarean section and hysterectomy rates - the two most common female operations today. The patient has taken a more central role in the decision making.

Patients are only to make wise choices if the correct and up to date data on benefits and outcome are clearly communicated to them. It is important that their health provider takes time to clarify the issues for them. It is important that the risks are enunciated in a realistic manner and using comparative every day risks as an example assists in this clarification.

Patients sometimes are misinformed by media, friends other medical practitioners and the new source, the internet. It is important that the patients attitude is understood so that expectations are not confused and unrealistic. It may be that the patient does not always reveal their biases and the origin of these sometimes unfounded concerns about their management and proposed surgery.

All these factors may limit the patients choice as a result. In fact, even evidence based medical information may have a significant and unnecessary limiting effect on choice.

A system of bargaining needs to ensue often with inevitable compromises. Trade-offs will always be a balance of improvement in quality of life versus risks versus patient preferences versus availability of service. These concepts are especially important when the choice of surgery, a hysterectomy, is such an elective decision, often patient driven.

In their article, Young and Solomon refer to the economics (the science of choice) of surgery. One of the best examples of this has been the development and implementation of the progesterone intrauterine device in the management of dysfunctional uterine bleeding, often a prime reason for hysterectomy request. The Pharmaceutics Benefits Advisory Committee looking at safety, efficacy and cost effectiveness quickly decided to reduce the costs to the patient of this new therapeutic device because of its obvious and immediate effect on reducing more invasive surgical methods of management.

Increasingly, surgical intervention will have to withstand the rigors of economic scrutiny at both government funding and private insurance funding levels. The contest of patient choice and evidence based resource allocation is most likely to be first recognised in the public hospital and health arena. It is clear that patient choices are already being eroded by restriction to access to theatre time and acute bed admissions in public hospitals. Private health insurers will have a greater say in these fund allocations in the future. This will inevitably modify choice for the patient, choice of operation, choice of hospital, choice of doctor and convenience choice. If rationing is to occur, who will be responsible? Will this be the new direction of pressures on surgical management of our patients for the future?

Summary

Hysterectomy has proven to be an effective method of management of very troublesome benign pathology in women's health. Often patients suffer considerably before they finally make their choice. It has been proven to be a safe low risk effective surgical treatment and continues to be improved. As we understand more about the disease processes, new treatment methods will be developed and with possible restriction of choice there will be perhaps a lower incidence in the future.

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Approach to patients with Peripheral Arterial Disease

Introduction

The most common cause of symptomatic obstruction in the peripheral arterial tree is atherosclerosis, a common problem facing general practitioners and cardiovascular physicians. This article will focus on atherosclerotic peripheral arterial disease (PAD), but other disease states affecting the peripheral circulation include atheroembolic syndromes, thromboangiitis obliterans (Buerger's disease), vasculitis, vasospastic disorders, popliteal entrapment syndrome, fibromuscular dysplasia and hypercoagulable states.

Our approach to the management of PAD utilises classification into four major groups: 1) asymptomatic PAD, 2) intermittent claudication, 3) chronic critical limb ischaemia (CCLI), and 4) acute limb ischaemia (ALI). CCLI describes patients with advanced chronic occlusive PAD often associated with local tissue damage. ALI is a medical emergency requiring immediate hospital admission to ensure early diagnosis and urgent limb-salvage intervention.

The prevalence of PAD increases with age; 2-3% at 60 years, increasing to 20-25% in people over 70 years of age. PAD occurs most often in elderly males with a mean age of 66 years: the ratio of men to women is 2:1. Although less common in younger persons, PAD is prevalent in patients over 50 years with common atherosclerotic risk factors.

PAD is usually considered an indolent, slowly progressive disease. The majority of patients are asymptomatic. About 70-80% of patients will have stable symptoms or become less symptomatic after 5-10 years. Progressive deterioration of claudication to rest pain or gangrene occurs in 3-5% patients annually and in 15-20% patients over 5-10 years. Amputation will be required in 1% annually and in 5-10% over 5-10 years. For patients with chronic critical limb ischaemia, the natural history and prognosis is similar to malignancy; within 12 months, 25% patients with CCLI will have had a major amputation, 20% will have died, leaving only 55% alive with both legs intact. Patients with diabetes are a unique sub-group; they have a high likelihood of developing critical limb ischaemia with an amputation rate seven times greater than in non-diabetic patients with PAD.

The natural history of patients with occlusive PAD is influenced by the extent of co-existent coronary artery and cerebrovascular disease. Fifty per cent of patients presenting with symptomatic PAD also have severe CAD with an overall reduction in life expectancy: in 10 years, 10-20% will have non-fatal myocardial infarction or stroke, and the mortality rate approaches 30%.

All patients with vascular disease should be assessed for risk factors. Tobacco smoking is the single most powerful risk factor for PAD; smokers have a six-fold increase in PAD incidence and 75 to 90% of patients are, or have been, tobacco smokers. PAD is 5 times more common amongst diabetics. Diabetic patients develop extensive and rapidly progressive disease at a younger age; typically multisegmental in distribution, with frequent involvement of the popliteal trifurcation and tibio-peroneal arteries, as well as sequential lesions within one arterial segment and potential collateral pathways such as the profunda femoris are more frequently involved. Dyslipidaemia increases the risk and the rate of progression of PAD. In hypertensive patients, the incidence of PAD is twice that of CAD and hypertension is present in 30 to 40% of patients with occlusive PAD. Systolic blood pressure appears to be a better predictor of PAD than diastolic blood pressure. More than 2 risk factors are found in 60-70% of patients and only 1% have no risk factors. Other recently recognised influencing factors include hyper-homocysteinaemia, infection/inflammation (CRP), genetics (lipoprotein a) and hypercoagulable states (eg increased fibrinogen).

Symptoms and Signs

The clinical presentation of patients with PAD is highly variable and depends on the involved vascular territory. It typically involves the superficial femoral

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and popliteal arteries, and occurs in older patients. Aorto-iliac disease tends to occur predominantly in younger patients.

Intermittent claudication is variably described as pain, tightness, aching, heaviness, cramping or discomfort of the lower limb musculature, occurring typically with exercise and resolving promptly with rest. It is consistently reproducible and the severity is measured in terms of the distance traveled before the onset of symptoms (usually constant). The sudden onset of severe limb symptoms or conversion of stable claudication to rest pain implies superimposed thrombosis, which invariably accompanies severe atherosclerotic PAD.

Calf claudication alone suggests superficial femoral artery and/or popliteal disease. Calf, thigh and buttock claudication suggests aorto-iliac disease. Isolated foot pain with ambulation may suggest infra-popliteal disease. Neurospinous conditions may be the cause of symptoms (pseudoclaudication) (Table 1) if the severity of the pain varies widely, or the pain does not subside quickly with rest, or if it is accompanied by numbness and paraesthesiae.

Symptoms related to PAD rarely occur until the vessel diameter has been narrowed by at least 50%. However, the presence of one or more lesions ≥50% does not imply that the patient will be symptomatic. Claudication is experienced by only 10-20% of patients with PAD, whereas 50% have atypical symptoms. Patients with complete occlusion of the major blood supply to a limb may have few symptoms if an ample collateral supply is present. Furthermore, subjective description of claudication may not be recongised due to exercise limitations: sedentary individuals with moderate to severe PAD may not experience claudication.

The most important sign of PAD is the diminution or absence of lower extremity pulses. For example, a normal common femoral pulse but absent popliteal and ankle pulses indicates occlusion of the superficial femoral or popliteal artery. The examination should include auscultation for bruits over the abdominal aorta, the common femoral arteries at the groin, the adductor canal and at the popliteal fossa, especially in diabetic patients. A reduced pulse with a loud bruit over that vessel indicates at least a 70% stenosis. A barely palpable pulse associated with a soft bruit indicates stenosis ≥90%. With complete occlusion, no pulsations or bruits are detectable, except for bruits in collateral vessels. There will be increased skin temperature in the region of the knee due to an expanded geniculate collateral circulation in response to SFA occlusion. The feet should always be inspected for skin integrity and wounds. Elevation of the legs at an angle greater than 60° and repeated flexing of the calf muscles (Buerger's test) produces pallor of the soles of the feet, followed by a rubor of reactive hyperaemia when the legs are placed in a dependent position, and indicates significant occlusive PAD.

Table 1 – Differentiation of claudication from neurospinous disease (pseudo-claudication)

	Claudication	Pseudo-claudication
Character of pain	Cramping, tightness	Weakness or clumsy
Location	Buttock, thigh, calf, foot	Back, buttock, hip, thigh, calf, foot
Exercise-induced	Yes	Yes or no
Distance to onset of pain	Same each time	Variable
Occurs with standing	No	Yes
Relief	Stop walking	Sit or change body position

Chronic critical limb ischaemia is characterised by rest pain, ulceration, skin necrosis or superficial gangrene. Rest pain is usually more severe at night and can only be relieved by placing the legs in a dependent position. However, prolonged dependency may cause oedema, further compromising the microcirculation, with delayed healing of ulceration. An ischaemic neuropathy, characterised by a severe lancinating or burning sensation in the leg and foot, may be superimposed and persist for many months even after correction of the ischaemia.

Clinical signs include skin atrophy accompanied by rubor and reduced skin temperature, hair loss, thickened nails with chronic fungal infection and poor nail growth. Ulceration occur mostly over areas subject to friction (toes, malleoli, heels), is typically necrotic and dry, extremely painful, with ill-defined and cyanotic borders and often covered with a black eschar (Figure 1). Most progress to gangrene and amputation if the circulation cannot be improved. Infection is typically polymicrobial (including anaerobes) but the classical signs of infection are often masked by poor circulation.

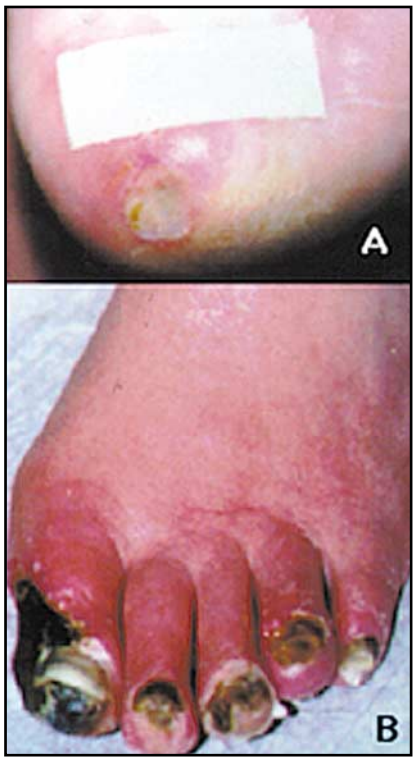

Figure 1: Critical limb ischaemia. *Clinical features of severe arterial insufficiency in a patient with critical limb ischaemia showing necrotic ulceration of the heel (A) and toes (B).*

Acute limb ischaemia occurs most often after thrombotic occlusion of atherosclerotic native arteries or bypass graft in-situ thrombosis. Embolic occlusion accounts for about 40% of cases; the source is cardiac (atrial fibrillation, post myocardial infarction, valvular heart disease) in over 75% of cases. Emboli may also originate from aneurysmal disease and atherosclerotic lesions of the thoracic or abdominal aorta.

Table 2 – Classification of acute limb ischaemia by clinical features

Category	Description	Capillary Return	Muscle Weakness	Sensory Loss	Arterial Doppler	Venous Doppler
Viable	Not threatened	Intact	None	None	Audible (AP >40mmHg)	Audible
Threatened	Salvageable if promptly treated	Intact, slow	Mild, partial	Mild, incomplete	Not audible (AP <40mmHg)	Audible
Irreversible	Major tissue loss, amputation	Absent (marbling)	Paralysis	Anaesthetic	Not audible (AP <40mmHg)	Not audible

AP= Ankle pressure

The clinical presentation is typically dramatic, with acute onset of severe pain, paraesthesiae, numbness and coldness, muscle tenderness and paresis. The extremity is cool, pale, and pulseless. A preceding history of stable claudication, abrupt shortening of the claudication distance and the finding of arterial bruits elsewhere, suggest thrombotic occlusion of a pre-existing arterial narrowing. Embolic events may have a subtle presentation with a cold or blue digit. A series of clinical categories with well-defined diagnostic criteria help determine whether the affected limb is viable, threatened, or already irreversibly damaged (Table 2). The presentation depends on the duration and level of occlusion, the status of the underlying vessels, and general factors (BP, cardiac output, presence/absence of diabetes, 0_2 saturation). The clinical status of the limb is a more reliable guide to viability than the time between event and presentation. Paradoxically, the patient with less underlying PAD often develops the most severe ischaemia; for instance, the patient with AF and normal peripheral vessels, who embolises to the common femoral or popliteal arteries. In contrast, the presence of better-developed collaterals in a patient with pre-existing PAD can be protective.

Investigations and Diagnosis

Assessment of PAD is obtained by non-invasive techniques to establish the diagnosis of PAD objectively, assess the severity of the disease, select appropriate management strategies, provide a prognostic guide and monitor natural progression.

The ankle-brachial pressure index (ABI), calculated from the ratio of ankle systolic pressure to brachial systolic pressure, gives a sensitive estimate of the degree of arterial insufficiency and usually correlates with functional symptoms. For example, an ABI of 0.7 – 0.9 would be consistent with mild-moderate arterial insufficiency. An ABI <0.50 signals the presence of CCLI. ABI alone does not indicate the level of disease and cannot differentiate stenosis from occlusion.

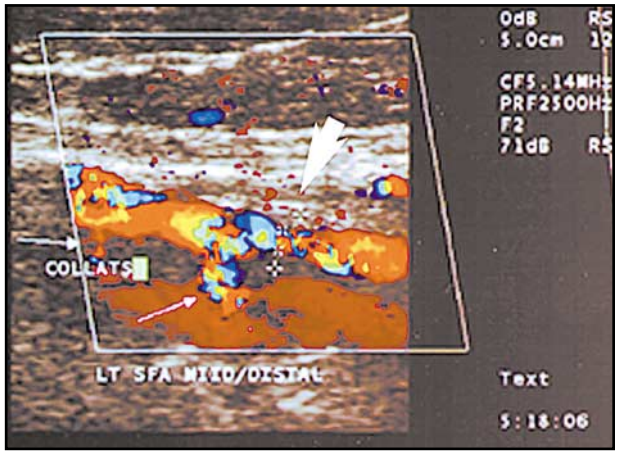

Figure 2: Duplex ultrasound.
Duplex ultrasound of the left superficial femoral artery in a patient with intermittent claudication showing a critical stenosis (arrowhead) in the adductor canal. Collateral vessels are also shown proximal to the stenosis (small arrows).

Doppler flow velocity waveform analysis is useful when pressure measurements may be invalid, for example in diabetics with calcified, non-compressible arteries (ankle pressure >240mmHg). A monophasic waveform indicates moderate to severe arterial insufficiency, whereas a multiphasic waveform excludes significant obstructive PAD.

ABI measurement has prognostic value in PAD. Ten-year survival rates for all cause mortality are 83% for ABI>0.85, 62% for ABI 0.4-0.85 and 44% for ABI<0.40. A patient with an ankle pressure index of ≤ 0.85 should be referred to a vascular medicine unit for evaluation and consideration of revascularisation.

Treadmill exercise testing allows objective assessment of functional limitations and can differentiate PAD from other causes of exercise-induced lower limb symptoms (eg neurospinous disease). If symptoms are reproduced without a drop in ABI, significant PAD is effectively excluded.

Duplex ultrasound scanning, using dual imaging and Doppler waveform analysis to assess anatomy and perfusion (Figure 2), provides an accurate anatomical description of arterial disease. Diagnostic angiography remains the time-honoured approach for diagnosis and assessment of obstructive PAD, and is an essential component of percutaneous revascularisation. Magnetic resonance angiography (MRA) has been increasingly used for assessment of the lower limb vasculature.

Management

The goals of therapy are to maintain functional status, reduce or eliminate ischaemic symptoms, and prevent progression of disease. A secondary goal is to reduce the incidence of coronary and cerebrovascular events.

General Measures

Ischaemic tissues tolerate infection poorly; the maintenance of skin integrity is important in patients with arterial insufficiency so meticulous foot, skin and

nail care, and good footwear are essential. Patients should examine their feet on a daily basis, looking for blisters, dryness, trauma, ulcers, tinea and areas of unusual skin discolouration. Dryness and fissuring of the skin around the heel predisposes to infection. The choice of appropriate foot-wear is important as most limb-threatening complications in patients with occlusive arterial disease arise from trauma – mechanical, chemical or thermal. In moderate arterial insufficiency, elastic compression stockings are to be avoided, as they reduce skin blood flow. Any infection needs to be treated early with appropriate antimicrobial therapy. Topical antibiotics are of no value and should be avoided.

Risk Factor Modification

The importance of aggressive control of risk factors remain fundamental to the medical management of PAD and decrease the rate of cardiac and vascular ischaemic events.

Patients who stop smoking have significantly better outcomes and cessation of smoking contributes to reducing re-occlusion rates following revascularisation.

Meticulous control of diabetes is paramount in reducing progression of atherosclerosis, reducing vascular thrombosis and limiting infected ischaemic lesions, which are typically resistant to treatment and not well tolerated. Diabetic patients also suffer from various neuropathies (sensory, motor, autonomic) that contribute to callous formation, shearing stresses, subcallous haemorrhage and infection, and ultimately ulceration; even minor foot lesions in diabetic patients should be treated vigorously.

Aggressive lipid-lowering therapy is indicated in patients with PAD.

Exercise

Regular exercise can double the claudication-free walking distance in patients with mild or moderate symptoms and stimulate development of collateral arterial circulation. Patients should be reassured that claudication pain does not represent damage to the limb. Patients should be encouraged to exercise for at least 30 to 60 minutes per day and to progressively increased levels.

Pharmacological Therapy

In contrast to the medical treatment for CAD, no pharmacologic agent has proved efficacious enough to produce significant improvement in symptoms of PAD to gain widespread acceptance or use.

Anti-platelet agents have been reported to decrease progression of atherosclerosis in occlusive PAD, but there has been no demonstrated improvement in exercise capacity. Clopidogrel has been shown to reduce the overall risk of ischaemic vascular events in PAD patients. All patients with PAD should receive antiplatelet therapy with at least Aspirin. Neither anticoagulant agents nor thrombolytic agents have been shown to be effective in chronic occlusive arterial disease.

Oxpentifylline (Trental), a rheologic agent, has been shown to increase walking distance by up to 21% over placebo. Patients most likely to benefit were those with moderately severe occlusive arterial disease (ABI<0.80) who have been symptomatic for more than one year. However, most investigators agree that Trental should not be considered as a substitute for exercise and risk factor modification in symptomatic PAD.

Management of Associated Disorders

All patients with reduced peripheral pulses and those being considered for revascularisation, with a history of past vascular events, symptoms of ischaemia or multiple risk factors for atherosclerosis should have assessment for myocardial ischaemia and left ventricular function as well as carotid artery disease.

Specific Measures for Chronic Critical Limb Ischaemia

All patients with CCLI should be referred for urgent vascular medicine consultation and where possible, admission to hospital. The limb must be placed in an arterial position. Topical nitrates improve skin circulation. Cessation of beta-blockers is recommended because of their potential to increase peripheral vascular resistance.

Provided there is no ulceration or necrosis, ambulation is beneficial because it encourages development of the collateral circulation. In patients with ulceration, exercise is restricted until ulceration has healed.

Heparin prevents arterial thrombosis and decreases the risk of venous thromboembolism that accompanies immobility and reduced limb perfusion in CCLI. Thrombolysis may be indicated in selected patients.

Prostaglandins by infusion have benefit in CCLI patients with intractable ulceration, frank gangrene prior to surgery (to accelerate demarcation) and for rapidly progressive ischaemia. Some ulcers heal quickly or demonstrate a marked reduction in size. The circulatory benefits, especially relief of rest pain, may continue for 6 – 8 weeks.

It is recommended that a revascularisation procedure be attempted if there is at least a 25% chance of saving a useful limb for at least one year.

Surgery or angioplasty in CCLI are essentially limb salvage procedures. An artery that remains open for only a few months may allow ulceration or necrotic lesions to heal. When a revascularisation procedure is not possible, primary amputation may be the only option to control spreading infection or gangrene, toxaemia, or rest pain. Sympathectomy is of limited benefit but some patients experience pain relief, perhaps due to interruption of pain fibres in afferent pathways.

Specific Measures for Acute Limb Ischaemia

Once the diagnosis is made on clinical grounds the patient should be immediately anticoagulated with heparin to prevent propagation of the thrombus, recurrent embolism and loss of valuable collaterals. Urgent angiography is indicated to determine the therapeutic options, including surgical or catheter-based thrombectomy, bypass, thrombolytic therapy, or direct percutaneous recanalisation.

If the limb recovers spontaneously, a conservative approach including anticoagulation and close observation for progression of ischaemia may be implemented initially. The limb, and especially the heel, should be protected against pressure injury and NOT elevated. Vasodilators are of no benefit

and may be deleterious if accompanied by hypotension.

Immediate surgical revascularisation is indicated in the profoundly or irreversibly ischaemic limb. Procedures include direct or suction embolectomy, endarterectomy or bypass grafting. Even with a favourable post-embolectomy limb salvage rate of 75 to 85%, 30-day mortality rate is about 20 to 30%, emphasising the co-existence of cardiac and other major arterial diseases in these patients.

Trials comparing intra-arterial thrombolysis to surgical intervention suggest that percutaneous catheter-based thrombolytic therapy may be an appropriate initial treatment of ALI, provided the limb is not immediately or irreversibly threatened. Ideal situations include thrombus in an atherosclerotic vessel or arterial bypass graft, embolism to a non-atherosclerotic limb, or when surgical intervention is contraindicated. In contrast to coronary thrombolysis, thrombolytic agents are infused directly at the site of occlusion in order to achieve dissolution of the large peripheral arterial thrombo-emboli. Using this approach, the underlying lesions can be further defined by angiography, and definitive percutaneous revascularisation can be performed immediately.

In selected patients, long-term management will include oral anticoagulation.

Interventional Therapy

Invasive therapy to restore pulsatile flow is the most effective treatment for the immediate relief of symptoms of PAD. Revascularisation is usually reserved for patients with progressive disease (increasing symptoms over 6 months) and those with severe or disabling symptoms that interfere with employment or lifestyle (claudication distance usually < 100m) in which exercise treatment has failed, except in two unique sub-groups: patients with diabetes who require an earlier and more aggressive approach on initial signs of deterioration given the propensity to develop CCLI and a higher rate of progression to amputation, and patients with acute limb ischaemia who require immediate revascularisation.

Once the indications for invasive therapy are clear and the anatomic substrate has been defined, the choice will be between conventional surgery and catheter-based techniques.

Surgical Therapy

Surgery typically involves placement of saphenous vein or prosthetic materials to bypass or substitute for the diseased native artery. Patency rates for surgical procedures at 5 years are 80-90% for aorto-bifemoral bypass, 60-80% for above-knee vein grafts, and 50-70% for below-knee vein grafts. The choice of surgical procedure is influenced by the distribution of disease, the adequacy of distal run-off vessels, and by co-morbidities. In some situations (aortic occlusion, common femoral artery bifurcation disease, and popliteal aneurysm), surgery remains the gold standard for revascularisation. Usually, these operations require general anaesthesia. They involve significant blood-loss and fluid-shifts in patients who may have profound involvement of other critical organ supply, thereby increasing operative morbidity and mortality. When possible, the use of catheter-based (endovascular) treatments provides a similar level of correction and durability, and substantially minimises risk and disability.

Lumbar sympathectomy

Lumbar sympathectomy is used alone in patients not fit for surgery or as an adjunct to aorto-femoral reconstruction. There is no good clinical evidence that lumbar sympathectomy increases graft patency or improves limb survival.

Endovascular Therapy

Major innovative advances have facilitated safer and more effective angioplasty over the last 3 decades. These include lower profile catheters (limiting complications related to vascular access), novel materials for balloon and guide wire construction facilitating passage through occluded vessels and endovascular stents that have dramatically improved both short-term and long-term outcomes. Subsequently, results have been overwhelmingly positive, and consequently percutaneous revascularisation has become increasingly popular as the first line of therapy for PAD. Innovations and improvements in imaging techniques have also resulted in better appreciation of the acute results of percutaneous interventions. Paramount among these has been digital enhancement of conventional contrast images and on-line intraprocedural imaging using intravascular ultrasound (IVUS).

Technical features, likelihood of success, and chances for clinical improvement, however, vary in degree according to the region of interest within the peripheral circulation. Weighted consideration of these individual issues is required to determine the appropriateness of non-surgical revascularisation.

Aorta and Iliac Arteries

Aorto-iliac revascularisation is recommended for: 1) Relief of symptomatic lower extremity ischemia, including claudication, rest pain, ulceration or gangrene, or embolisation causing blue-toe syndrome; 2) Restoration and/or preservation of inflow to the lower extremity in the setting of pre-existing or anticipated distal bypass; 3) Procurement of access to more proximal vascular beds for anticipated invasive procedures (e.g., cardiac catheterization/PTCA, intra-aortic balloon insertion); and 4) Rescue flow-limiting dissection complicating access for other invasive procedures.

Over the past 20 years, revascularisation strategy for aorto-iliac disease has changed significantly. A three-fold increase in aorto-iliac Percutaneous Angioplasty (PTA) and a concurrent decrease in aorto bifemoral bypass grafting have been noted. However, in spite of the changing patterns and overwhelming evidence (*vide infra*) supporting a less invasive strategy of balloon angioplasty (with or without stenting) considerable controversy still remains in some circles concerning the "optimal" treatment with inter-ventionalists generally supporting a primary strategy of angioplasty and stenting and vascular surgeons generally supporting a more traditional approach

of "definitive" revascularisation with aorto-bifemoral bypass, especially in young patients or those with advanced or diffuse disease.

PTA is generally used for more focal disease of the distal aorta, common iliac arteries and external iliac arteries. The results of balloon angioplasty for stenotic lesions are excellent, with acute technical and clinical success in excess of 90% and 5-year patency rates approaching 85%. Factors associated with good results include short, focal lesions; large vessel size; common iliac (as opposed to external iliac); single lesion (as opposed to multiple serial lesions); male gender; claudication as opposed to critical limb ischemia; and the presence of good runoff. The results in patients with diffuse disease, smaller vessels, diabetes mellitus, female gender, critical limb ischemia, and poor runoff are less favourable. Nonetheless, patients in these categories may still benefit from PTA.

PTA can also be performed for aortoiliac *occlusions* with initial technical success rates between 70% and 98% and 3 year patency rates approaching 85%. Thrombolytic therapy, hydrophilic guide-wires and advancing catheter technologies have led to an increased ability to primarily traverse even lengthy, chronic occlusions.

Endovascular stents (and stent-grafts) have dramatically changed the short-term (90-100% technical success) results by improving the immediate haemodynamic results of PTA and long-term results (75-90% 5-year patency) of PTA by effectively managing recoil and PTA related flow-limiting dissections, particularly in chronic iliac artery occlusions. This compares favourably with results of surgical recanalisation of aortoiliac disease. However, in the best of surgical hands, mortality rate for these patients with high likelihood of coexisting coronary artery disease is 2-3%, associated significant morbidity notwithstanding. Accordingly, the threshold for surgical intervention has remained high and usually reserved for patients with critical limb ischemia, or advanced degrees of disability. Hence, for complex aortoiliac stenoses and occlusions, PTA followed by stenting is now the preferred primary therapy of most interventionalists (Figure 3).

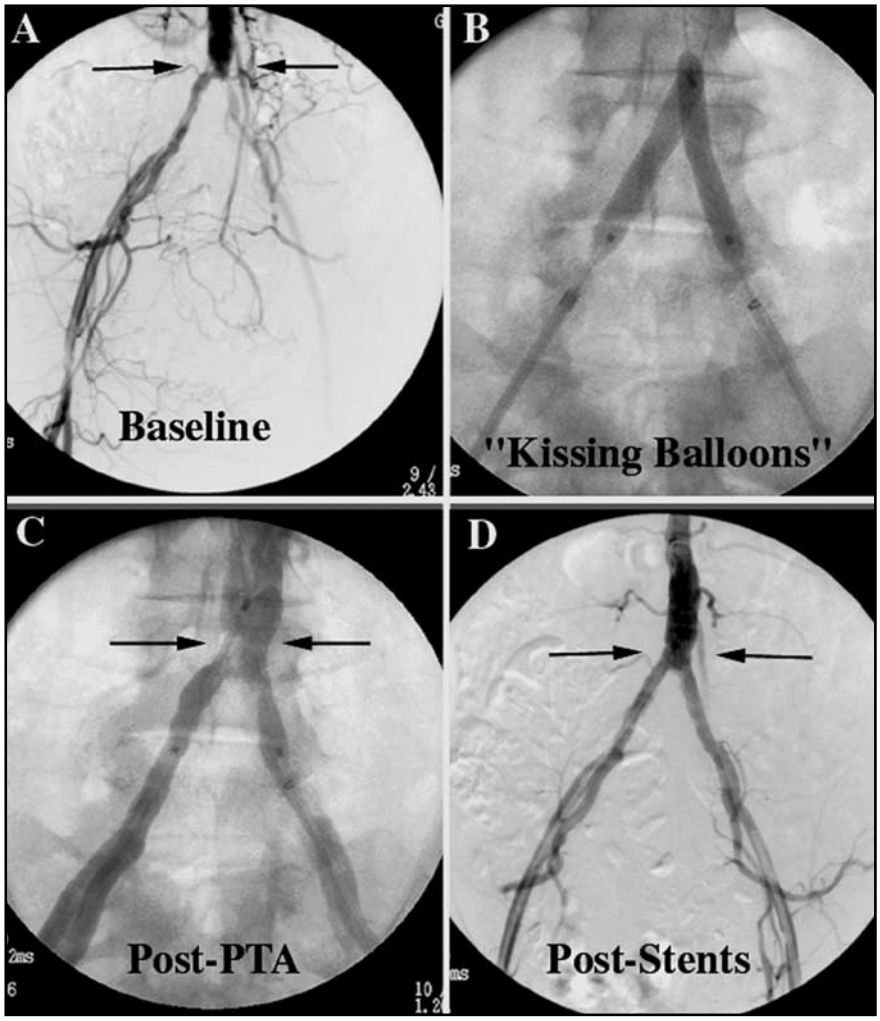

Figure 3: *Iliac revascularisation*
Percutaneous revascularization of bilateral common iliac lesions in a patient with disabling buttock and thigh claudication, and chronic myocardial ischemia. (A) Baseline angiography demonstrates bilateral common iliac ostial stenoses (arrows). (B) PTA using "kissing balloons". (C) Residual lesions (arrows) with dissection following PTA. (D) Deployment of "kissing stents" resulted in normal patency of iliac vessels (arrows) and excellent distal flow with abolishment of pressure gradients. Percutaneous revascularisation avoided potential high morbidity/mortality associated with surgical reconstruction.

Superficial Femoral (SFA) and Popliteal Arteries

The balance of revascularisation therapy is shifting towards a predominantly percutaneous approach in this group. Even occlusive disease is now not considered beyond the realm of angioplasty. In patients with severe claudication or rest pain, PTA may be less risky than conventional surgical reconstruction. In patients with non-healing lesions and/or threatened limb loss in whom the risks of surgery are considered prohibitive, or in whom veins are unavailable for distal bypass, PTA of even lengthy, occluded segments may facilitate healing.

The results of balloon angioplasty for stenotic disease have improved over time with respect to the acute results, now approaching 95-100% acute technical success and 5-year primary patency rates up to 70% have been reported. The success rate of crossing occluded segments has also risen, thus ensuring an increasing acute technical success, now approaching 95% (Figure 4). However, primary long-term patency is considerably less, in the range of 40-50%.

An important caveat in the management of patients with symptomatic SFA/popliteal disease is the issue of restenosis, which may complicate the clinical course of as many as 50% of patients undergoing PTA. The cause of the high restenosis rate is an enigma and its occurrence raises fundamental questions as to whether the biology and patho-physiology of plaque formation in the SFA/popliteal is in some way different from that in other vessels. Several promising strategies lie

on the horizon, including firstly, gene transfer of angiogenic cytokines to accelerate re-endothelialisation of the disrupted endovascular surface and inhibit intimal hyperplasia, thereby reducing restenosis, and secondly endovascular brachy-therapy in conjunction with SFA/pop PTA is associated with reduced restenosis rates in early phase 1 trials.

The documented benefits achieved by using endovascular stents in the SFA has been less favourable. At this time, stents are deployed for acute treatment of a flow-limiting dissection and for failed balloon angioplasty, usually in the setting of eccentric stenoses, long-segment stenoses (and occlusions), and stenoses due to intimal hyperplasia at graft anastomosis. Stents should preferably be of the self-expanding variety. Balloon-expandable stents should particularly be avoided within the adductor canal. However, while the immediate and early results have been excellent, restenosis caused by intimal hyperplasia in the stented segment is quite common in the first 3-6 months. Studies from a variety of stent designs in the SFA have shown variable restenosis rates; primary 1-year and 3-year patency rates were in the range of 22-81% and 18-72% respectively. Furthermore the use of stents in the SFA has been complicated by an unpredictable incidence of sub-acute thrombosis, and thus uncertainty regarding the need for short-term, and even possibly long-term, anticoagulation. Clopidogrel should be considered for 6-12 months following stent deployment as it appears to significantly reduce restenosis rates (P. Vale, unpublished data).

A variety of other technologies have been investigated as means of improving long-term patency in the SFA. *Directional atherectomy* (DA) has been used in short, eccentric lesions resistant to balloon dilation, and for fibrotic lesions with significant recoil (e.g., graft anastomoses) but has no role in reducing restenosis. *Rotational atherectomy* has not thus far been demonstrated to have an advantage for SFA/popliteal revascularisation. The role of *laser angioplasty* in SFA/popliteal revascularisation remains controversial and unproven. No trial has thus far demonstrated definitive benefit of this device at this level.

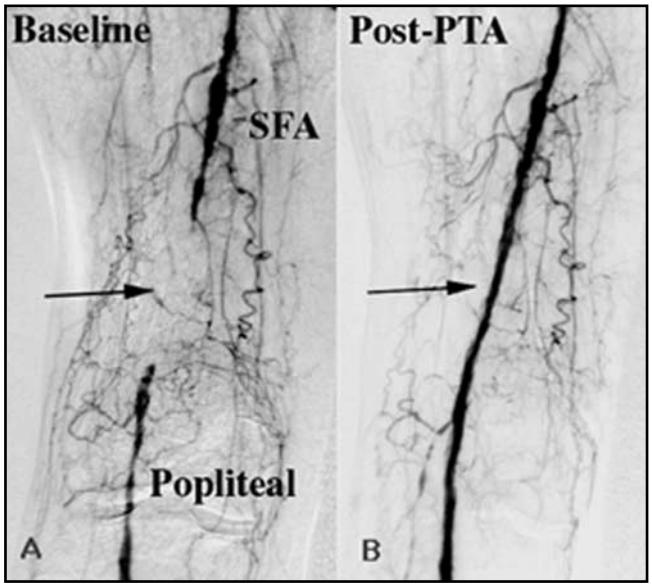

Figure 4: Percutaneous revascularisation of femoral occlusive disease.
A: *DSA image of a patient with disabling claudication showing an occluded superficial femoral artery (SFA) and popliteal artery with numerous collateral vessels.*
B: *Post-PTA. DSA image of the same patient percutaneous revascularisation showing restoration of patency with balloon angioplasty alone.*

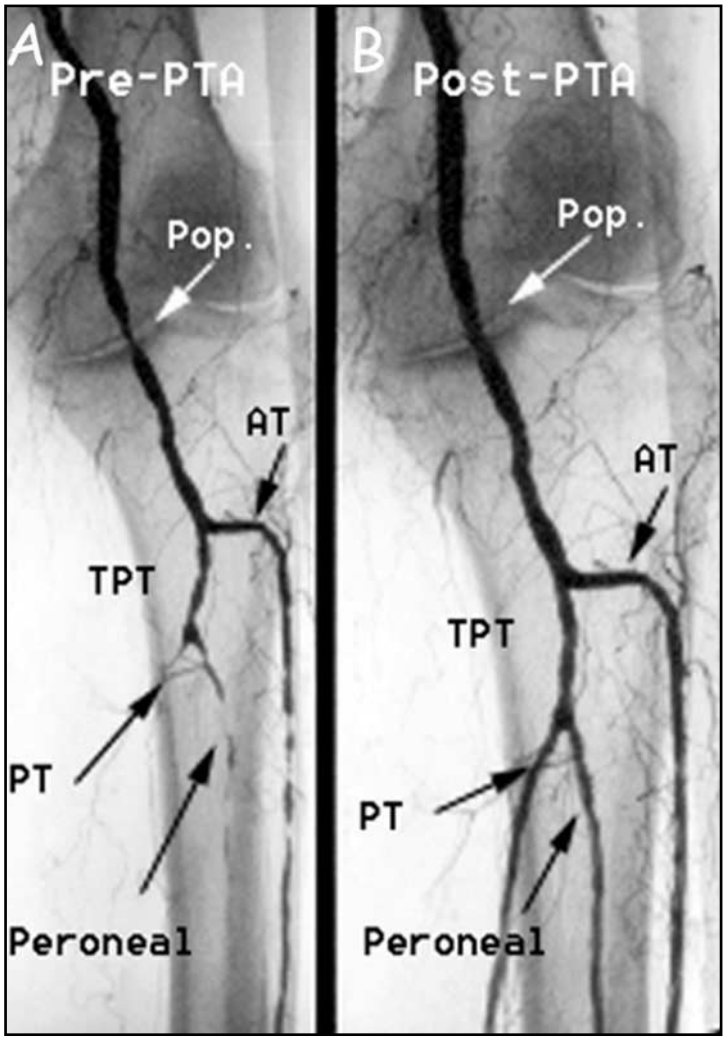

Figure 5: Limb salvage angioplasty.
A: *Pre-PTA. Digital subtraction angiography image of the left lower leg showing 50% stenosis of the popliteal artery, 50% stenoses of the tibio-peroneal trunk, occluded posterior tibial artery, occluded peroneal artery and subtotal occlusion of the anterior tibial artery.*
B: *Post-PTA. Digital subtraction angiography of the same patient following percutaneous revascularisation of the popliteal artery, tibio-peroneal trunk and all three infrapopliteal run-off vessels, with restoration of antegrade flow to the foot.*

Infrapopliteal Arteries

Claudication is rarely due to isolated disease of the infrapopliteal arteries. Patients with critical limb ischemia due to infra-popliteal disease often undergo bypass surgery, but regardless of the conduit (reversed vein, in situ vein, or prosthetic material) patency rates are nonetheless inferior to those of more proximal reconstruction. Many of the patients treated with infra-popliteal angioplasty to date have been those who were too high risk or otherwise unqualified for bypass surgery. It is conceivable that the long-term clinical outcome of percutaneous therapy may ultimately equal that of distal bypass grafting. Over the past decade, reports have documented that stenotic and even short occlusions of one or more infrapopliteal arteries can be revascularised percutaneously with a high degree of efficacy and at extraordinarily low risk, particularly for critical limb ischemia as opposed to claudication (Figure 5). These studies have demonstrated technical and clinical success rates in the range of 80 to 95% (the success rate in stenoses is superior to that in occlusions). Endovascular stents are not recommended for infrapopliteal vessels.

It must be emphasised that the goals of infrapopliteal PTA often differ from those of above-the-knee therapy and vary with clinical presentation. In most patients with claudication, for example, below-knee angioplasty is not necessary, as treatment of co-existing proximal disease alone is often sufficient for symptomatic relief. There is a subset of patients who claudicate due solely to infra-popliteal disease, for whom PTA is becoming more popular. Such a strategy should be reserved, at least for the present, for patients who have severe symptoms. Infrapopliteal PTA may also be justified in claudicants who undergo proximal revascularisation (either with surgery or PTA), in whom the runoff is severely impaired, as outflow may be the principle determinant of long-term patency for femoro-popliteal revascularisation.

In patients with rest pain or ischemic ulceration, restoration of uninterrupted patency of at least one of the three major infrapopliteal arteries is generally required to obviate symptoms and/or heal a distal ischemic lesion or salvage the limb (Figure 6). In this group of patients, aggressive application of PTA may achieve extremely gratifying results, even in patients with calcified and/or lengthy total occlusions. Once healed, most patients will do satisfactorily, even in the face of documented reocclusion or restenosis. However, the incidence of restenosis – which remains high – should not be a factor in the decision to employ a percutaneous approach for what is, in many of these patients, a short-term problem.

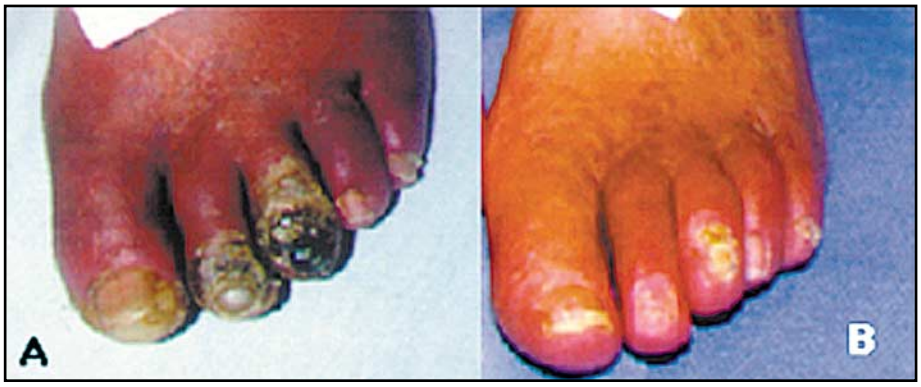

Figure 6: Early revascularisation is essential for limb salvage.
Figure 6A: *Critical limb ischaemia with threatened foot. A 72-year-old diabetic male with necrotic ulceration of three toes, ischaemic rubor, atrophic skin and loss of hair*
Figure 6B: *The foot of the same patient taken at four months following percutaneous revascularisation (see figure 5) showing healing of necrotic ulceration and improved skin colour.*

Conclusions

The spectrum of thresholds for referring patients with PAD is very broad, ranging from practitioners who only refer patients with advanced ischaemia, to those who consider lifestyle-limiting claudication grounds for considering revascularisation. In the past, there was little reason to perform diagnostic angiography unless surgery was indicated. Given the risks of major reconstructive surgery in a high-risk population with coronary and cerebrovascular disease, restricting surgery to patients with altogether disabling claudication or threatened limb loss was justifiable. Now, intervention at an earlier stage of symptomatic disability is possible as percutaneous revascularisation has markedly improved outcomes for patients with PAD.

In the future, invasive therapy for PAD will continue to shift toward a predominantly percutaneous, as opposed to surgical, approach for selected patients. As interventions become more effective and safe, the threshold for treatment will be lowered and the number of percutaneous interventions will rise. For patients who have had to opt for amputation in the absence of viable options for conventional revascularisation, the possibility of encouraging the formation of new vascular conduits by introducing angiogenic factors or stem cells may offer new hope for limb salvage.

Neurosurgery – Minimal or Maximum Exposure: The Modern Evolution

Dr J.P. Sheehy

Introduction

The ability to image the brain has been revolutionised in recent years with the advent of magnetic resonance imaging and high definition computerised tomography. This imaging information alerts the clinician with great accuracy to the site of the tumour and important anatomical relationships, which assists in surgical planning. Concurrently, with the increased sensitivity of neurological imaging has come a revolution in surgical technique which in some cases has produced a major minimalisation of technique and, in others, maximal exposure has been the appropriate choice.

Discussion

Minimalisation of intracranial surgery has involved an increasing use of the endoscope, especially for intraventricular surgery, and also a significant minimalisation of the conventional pituitary transnasal operation and I shall address this in greater detail. Conversely, for tumours arising in the region of the tentorium, cavernous sinus, sphenoid wing and anterior clinoidal region, a key principle has been minimal manipulation of the brain. For this to occur, the exposure has become much larger to ensure brain protection.

Minimal Exposure

The initial surgical intervention for pituitary tumour was by craniotomy. In the late 19th century the procedure carried a high mortality. In 1912, Cushing[1] advocated transsphenoidal surgery. It was reintroduced in its modern form in the 1960's by Guiot in Paris and Jules Hardy[2] in Montreal. The original transsphenoidal operation involved removal and subsequently mobilisation of the nasal septum, at times with significant nasal and dental morbidity. Recent changes in the surgical approach involve cannulation of one nostril and no longer involve any surgical interference with the anterior two-thirds of the nasal structures. The operation is now performed by opening directly into the sphenoid sinus and using the operating microscope to obtain a direct view of the pituitary tumour. The endoscope can play a role in this procedure, especially in identifying extension of the tumour into the cavernous sinus.

Figure 1 illustrates the conventional approach and Figure 2 the modern approach with detachment of the septum from the anterior aspect of the sphenoid using uni-nostril cannulation and the operating microscope for access. The advent of frameless computer-directed stereotaxy[3] makes this minimal approach anatomically accurate and safe for the patient. The stereotactic system relies on a camera which sees a pointer placed on the skull base. The position of the pointer and its relationship to the tumour is displayed on a television screen in the operating room.

The nasal disturbance in transsphenoidal surgery is now very minimal. The use of the microscope, stereotaxy and endoscopic assistance makes this minimal operative approach very accurate and safe for the patient.

Maximal Exposure

The treatment of tumours involving the tentorial edge, the medial middle fossa, the cavernous sinus and the region of the optic nerve and clinoid has been limited by conventional techniques, which involve significant brain retraction and morbidity in treating these lesions. Recent changes in approach have made removal of these lesions much safer for the patient. This has been achieved by restricting the amount of brain manipulation and to ensure this, a maximal opening in the base of the skull has been undertaken. The orbitozygomatic opening[4,5] has been a significant advance in facilitating a lateral and basal skull opening. It can be used alone or in conjunction with petrous and other basal openings as described initially by Fisch.[6] These exposures are frequently a combined procedure undertaken with my skull base colleague, Professor Paul Fagan. The technique of orbitozygomatic crani-

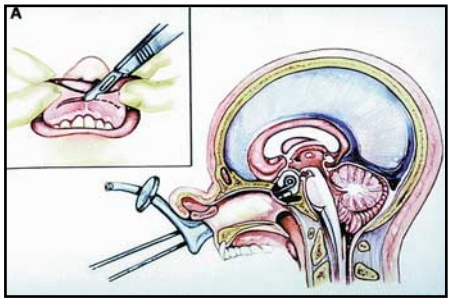

Figure 1: *The original sublabial mid nasal operation for pituitary tumours*

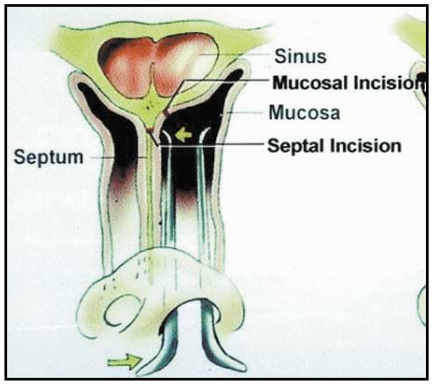

Figure 2: *The new approach for pituitary through one nostril and with no disturbance of the septum*

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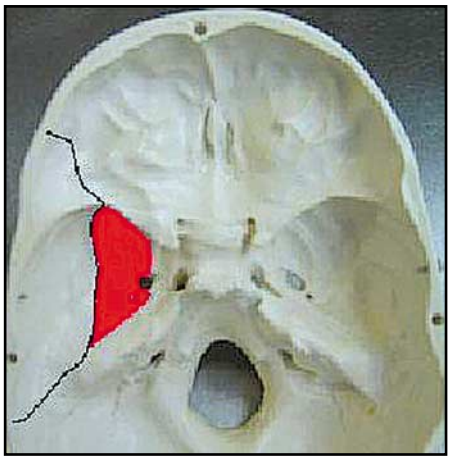
otomy involves removal of the lateral wall of the orbit, the zygomatic process of the frontal bone, the zygoma, and the zygomatic process of the temporal bone as a single piece. The floor of the middle fossa can then be removed up to the foramen rotundum or foramen ovale or medial to these structures, depending upon the direction of surgical approach. Figure 3 demonstrates this bony opening. This illustration demonstrates that the approach is below the brain and allows for minimal brain retraction. Figure 4 (a-c) demonstrates tumours which have been removed by the orbitozygomatic approach.

a. Meningioma of the tentorial edge indenting the mid-brain.
b. Meningioma involving the medial middle fossa and extending superiorly.
c. Meningioma in the middle and posterior fossa extending across the petrous apex.

The morbidity of this approach is very low. There have been no cases of infection. The cosmetic result is excellent as microplating systems reconstruct the zygoma and orbit in normal anatomical positions.

Conclusion

The revolution which has occurred in the ability to image and anatomically localise brain tumours has markedly increased the operative safety for our patients. A significant factor in this increased safety has been a change in operative approach: in some circumstances a very minimal opening with microscopic and computer assistance is best; in other circumstances, a major opening of the base of the skull protects the brain and enhances outcome.



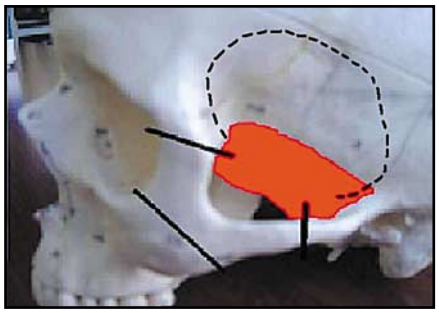


Figure 3: *Illustrating the removal of the zygoma, orbital wall, temporal squama and bone of medial middle fossa floor (red shading) in orbito-zygomatic craniotomy. (Drawn by Dr Owyang)*

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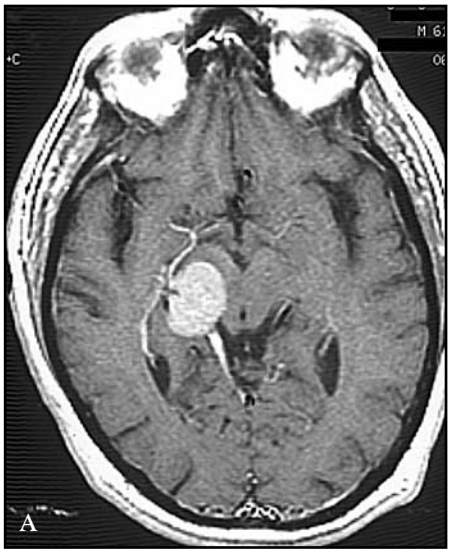

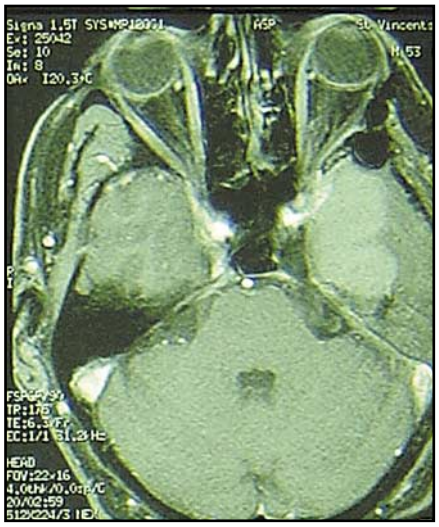

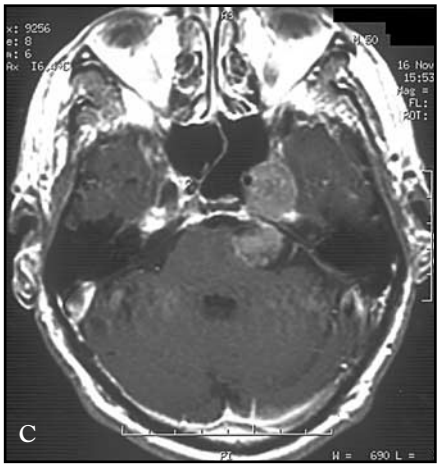

Figure 4: *Illustration of 3 different meningiomas (a-c) removed via skull base surgery as per text.*

Dr Adrienne Morey

The Pathologist's Role in Molecular Targeted Therapies: FISHing for Diagnostic and Prognostic Information

Introduction

We are entering a new area of targeted chemotherapy. Hundreds of new drugs are under development which target specific pathways in tumour development, seeking to inhibit molecules which are upregulated during tumour growth. The aim is a more effective therapy with less generalised side effects. Several such drugs including imatinib (Glivec™} (a bcr-abl & c-kit tyrosine kinase inhibitor which is used in the treatment of certain leukaemias and stromal tumours of the gastrointestinal tract) and trastuzumab (Herceptin™) (a humanised antibody to the HER-2 receptor overexpressed in a proportion of breast cancers) are already in relatively widespread use in Australia.

The anatomical pathologist is increasingly being required to determine whether a patient's tumour is likely to respond to these targeted (and costly) therapies. Accurate patient selection is crucial for maximizing effect while minimizing impact on the health care budget. This is necessitating the adoption of new techniques which combine morphology with molecular classification, one of the best examples of which is FISH (Fluorescent in situ hybridisation).

This technique involves the localization target DNA in cells or tissue sections via the hybridization of a specific complimentary DNA probe, labelled with a fluorescent dye. Multiple probes labelled with contrasting fluorochromes can be applied simultaneously, then each examined under light of the appropriate wavelength, the result being analysed with digital imaging software. **(Figure 1)** The technique can be applied to either

fresh tissues (as has been traditionally performed in cytogenetics laboratories) or paraffin sections, allowing retrospective diagnosis on material obtained many years ago.

In Anatomical Pathology, SydPath we have been extensively involved in the application of FISH techniques to paraffin sections. While the technique has application to many different solid tumours and haematological malignancies (for instance, detecting specific diagnostic chromosomal translocations), the two areas we have been most heavily involved in are the identification of breast cancers with HER-2 oncogene amplification, and the analysis of oligodendroglial brain tumours to determine potential chemosensitivity.

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HER-2 Gene Amplification in Breast Cancer

HER-2 (also known as c-erbB-2 and neu) is a cell surface receptor which, when stimulated, leads to activation of intracellular pathways involved in gene transcription and cell cycle regulation. It is normally present in benign breast tissue at a low level, as well as in several other organs. Around 20% of breast cancers have extra copies of the HER-2 gene ("gene amplification"), resulting in extra copies of the HER-2 protein on the cell surface ("overexpression"). Overexpression of HER-2 is in itself a poor prognostic factor, however these extra copies are targets for the drug trastuzumab (Herceptin), which is a humanized monoclonal antibody which binds to HER-2 and inhibits its role in cell growth and division. This drug has been shown to improve survival in patients with metastatic breast cancer whose tumours overexpress HER-2, but is ineffective against tumours which do not. Government funding has been made available to provide the drug to eligible patients. Given the expense of the drug and the potential for side-effects, accurate patient selection is crucial.

Nowdays, nearly all breast cancers are routinely tested by the pathologist to see whether they overexpress HER-2 at the time of initial surgery. This is usually done by using an immunohistochemical stain on a section of the paraffin-embedded tumour, similar to the way testing for oestrogen and progesterone receptors has been done for many years. Although relatively inexpensive and quick, this test is not always easy to interpret, and can be affected by the way the tissue has been fixed and processed. Around 20% of cases will have an "equivocal" result, and require further testing. The current "gold standard" for assessing such equivocal cases is FISH. Normal cells should have only two copies of the HER-2 gene; tumour cells with HER-2 amplification will have multiple copies. A control probe for the centre of chromosome 17 (the chromosome on which HER-2 is located) labelled with a contrasting dye is used to control for cell ploidy. **(Figure 2a,b)**.

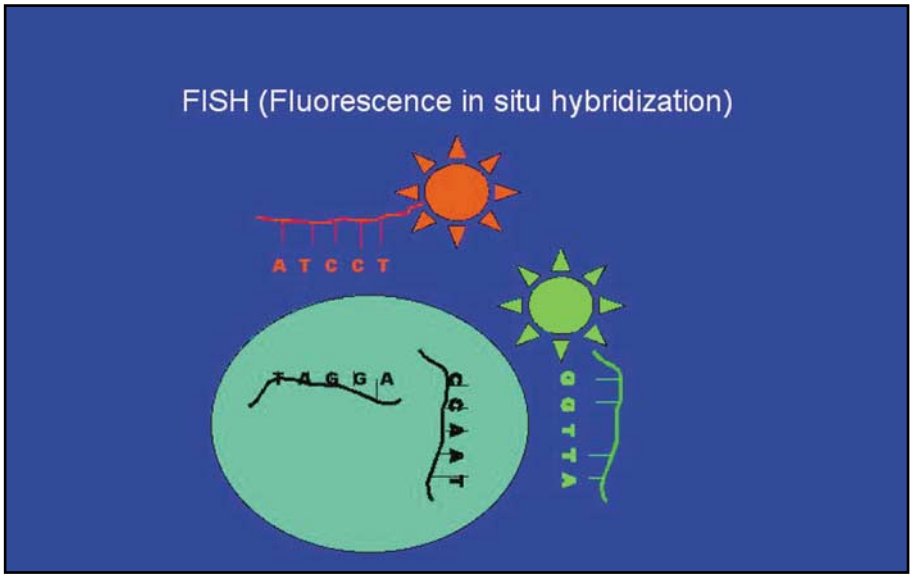

Figure 1: *Dual probe FISH: two different targets are detected by co-hybridization of probes labelled with different fluorochromes.*

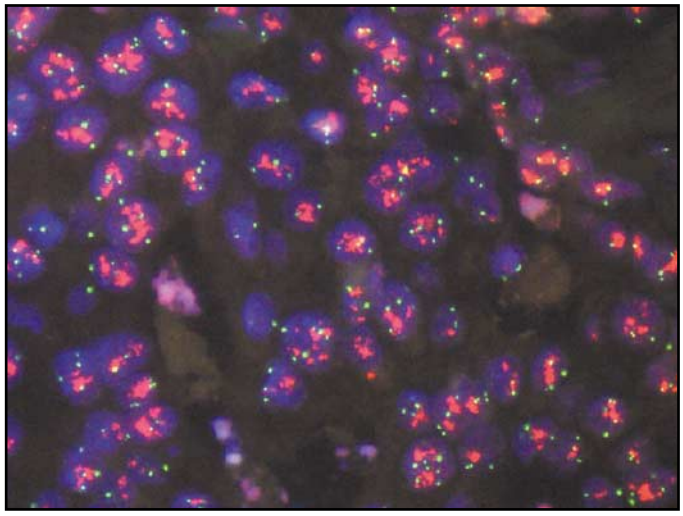

Figure 2a: *Breast carcinoma with HER-2 amplification (numerous red signals per cell) compared to chromosome 17 centromere control (green signals).*

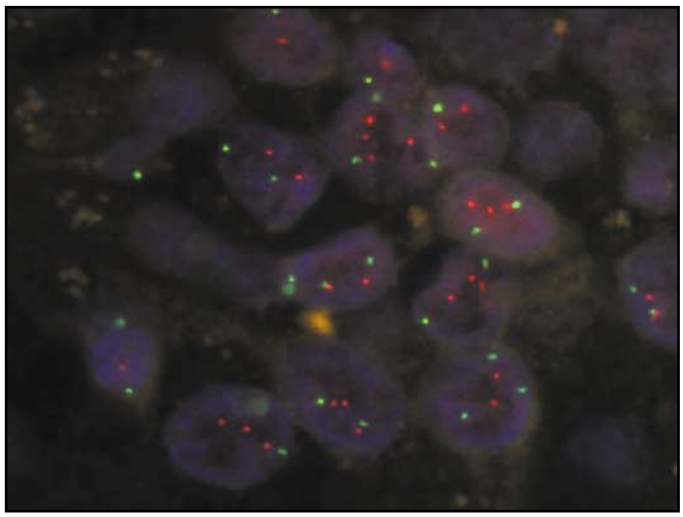

Figure 2b: *Breast carcinoma showing no evidence of HER-2 amplification (red signals = green signals.*

At SydPath we have been involved in providing a national reference service for FISH testing cases of breast cancer with equivocal HER-2 immunohisto-chemistry. To date we have tested over 2500 cases from all around Australia, referred by over 70 different pathology practices. About a quarter of the "equivocal" cases show evidence of true HER-2 gene amplification by FISH, and this knowledge helps the oncologist plan appropriate treatment. The experience gained in providing this reference service has allowed us to develop technical expertise unparalleled in Australia, and to extend the paraffin FISH technique to other clinical questions.

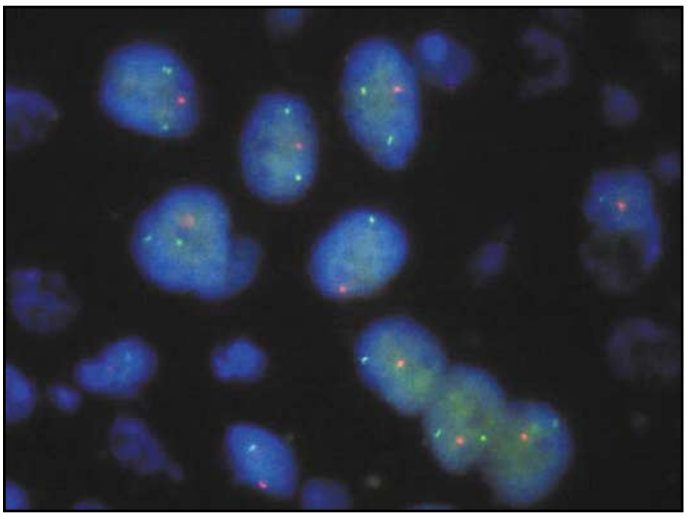

Figure 3a: *Analysis of chromosome 1p(red) vs 1q (green) in 60 cells from an oligodendroglioma shows a ratio = 0.63 indicating 1p loss.*

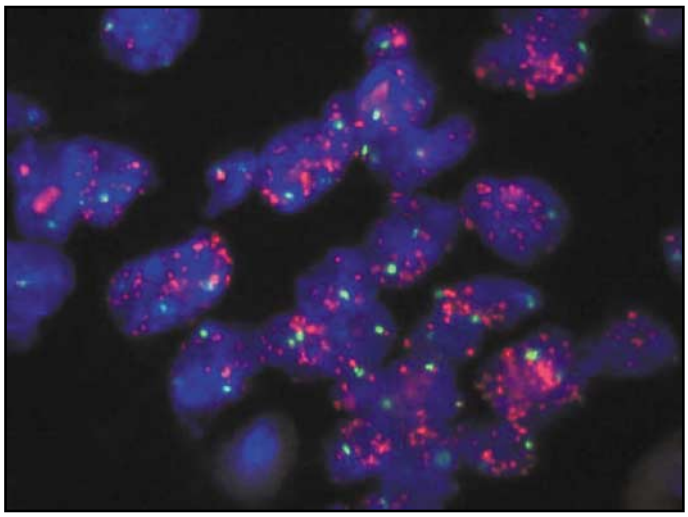

Figure 3b: *Amplification of EGFR-1 (red) compared to chromosome 7 centromere (green) in a small cell glioblastoma multiforme.*

Analysis of Chromosomal Loss in Oligodendrogliomas

Malignant gliomas are characteristically grouped into oligodendrogliomas, astrocytomas, ependymomas and mixed glial tumours. They vary in grade from WHO II to IV and are the most common of the primary brain tumours. For many years it has been recognised that a subgroup of patients with anaplastic (Grade III) oligodendrogliomas have an unusually favourable response to chemotherapy however, until recently, there has been no clinical or histological means of identifying potential responders. Sometimes it is even difficult to distinguish between the different tumour types on routine stains, as there are no specific markers for oligodendroglial tumours, and a "small cell glioblastoma" may mimic an anaplastic oligodendroglioma.

Recent molecular analysis has demonstrated that loss of heterozygosity (ie, loss of a single copy) of the short arm of chromosome 1 (1p) and the long arm of chromosome 19 (19q), are frequently associated with the formation of oligodendrogliomas. Combined loss of 1p and 19q has been shown to be associated with longer survival and to predict for chemoresponsivenss in anaplastic oligodendrogliomas. Assessment of 1p/19q loss in glial neoplasms is therefore becoming crucial for clinical decision-making, in order to target chemotherapy at those patients who are likely to respond.

Fluorescent in situ hybridisation has several advantages over other methodologies for assessment of 1p/19q loss. For instance, it is applicable to archival paraffin-embedded tissues, and there is no necessity for an additional comparative blood sample. Using FISH analysis (rather than methodologies involving extracted DNA), analysis can be limited to tumour cells, avoiding "contamination" of the result by inflammatory and stromal cells.

We have analysed nearly 100 brain tumours for 1p/19q loss by FISH to date, with cases referred from both the St Vincent's campus and other teaching hospitals in Sydney. Using contrasting colour probes to loci on both the long and short arms of chromosomes 1 and 19 respectively, we have confirmed dual loss of 1p and 19q in the majority of tumours with obvious oligodendroglial phenotype; loss of 1p is detected by the presence of only around half as many 1p signals compared to 1q signals **(Figure 3a)**.

In addition to the use of probe pairs for 1p/1q and 19q/19p, the addition of a third probe pair for EGFR-1 (epidermal growth factor receptor-1, or HER-1)/chr7 has proved a useful means of helping to distinguish between anaplastic oligodendroglioma and small cell glioblastoma. **(Figure 3b)**. EGFR-1 is amplified in a high proportion of "primary" glioblastomas (often with "small cell" morphology), and is associated with a non-chemoresponsive phenotype. The addition of this probe can therefore assist both classification of difficult tumours, as well as prediction of likely chemosensitivity.

Unfortunately, there is currently no Medicare rebate for FISH performed on paraffin sections; a case of the benefit schedule lagging behind clinical necessity.

Conclusion

Accurate tissue pathology is the mainstay of cancer diagnosis and provides the basis for prognostication and treatment planning. However, novel targeted therapies require targeted molecular testing. Classification by standard morphology alone is becoming insufficient in a range of different malignancies. The incorporation of molecular tests into "routine" histopathology is one of the most exciting challenges facing pathologists today and is an area regarded by pathologists at SydPath as a crucial and expanding part of our diagnostic service.

Dr John Kennedy

The Evolution of Modern Cataract Surgery

Introduction

One hundred years ago, at the 1905 American Academy of Ophthalmology and Otolaryngology meeting, Dr D.W.Green pronounced: "A well conceived and properly executed cataract extraction is probably the acme of surgical skill. No other surgery approaches it in definiteness of conception, delicacy of execution and lastly the contentment and joy it has brought to humanity. Other surgeries relieve suffering, some prolong life, and some correct deformity, but the extraction of the opaque lens does all of these and more."

Dr Green was probably prone to hyperbole, but his sentiments ring very true today, and in fact over the past 25 years advances in technology have transformed cataract surgery into one of the safest, most beneficial and cost effective surgical procedures carried out today.

In 2004 in Australia there were about 140,000 cataract operations performed – the need for surgery will double over the next 20 years with the ageing population.

By age 60 about 20% of people have signs of cataract – this rises to over 80% by age 80. It's been said that everyone will develop a cataract if they live long enough.

Cataract is one of the "big four" causes of visual morbidity in Australia – the others are glaucoma, age related macular degeneration and diabetic retinopathy.

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Cataract and Its Presentation

Cataract is a general term for any opacity in the lens (Figure 1a) -this is a normal part of ageing. There are other secondary causes -congenital, traumatic, hereditary conditions (eg myotonic dystrophy) and drugs, especially steroids. At St Vincents a special group of patients are the heart and heart/lung transplant recipients, many of whom are on high dose steroids for a prolonged time and they frequently develop posterior subcapsular cataracts (Figure 1b) needing surgery.

The lens in the eye lies behind the iris (Figure 2). Its principal role is to help focus light onto the retina, and normally the lens is optically clear. As a cataract develops the patient notices that vision gradually becomes more and more blurred (Figure 3), and colours seem "washed out". A good description is that it's like looking out through a dirty window. This usually happens at much the same rate in both eyes. With time vision becomes dimmer, and eventually the patient becomes blind, either due to the cataract itself or other secondary complications such as phacolytic (lens induced) glaucoma.

The decision for surgery is dependent on a number of factors, with surgery usually being recommended when the symptoms begin to interfere with the

Figure 1a

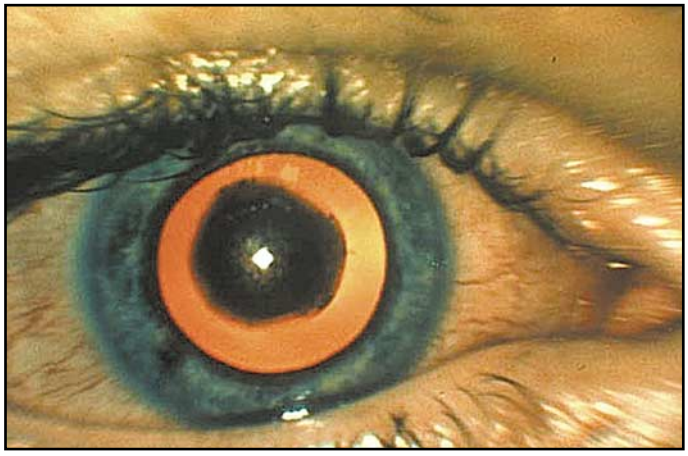
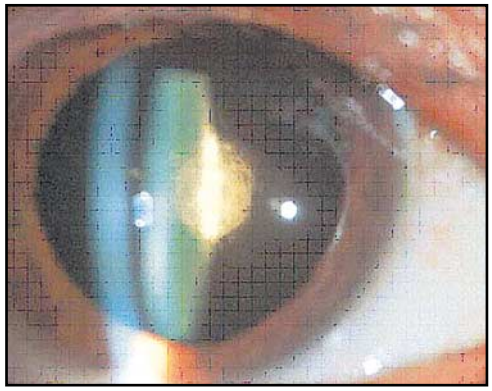


Figure 1b



patient's lifestyle or work. An important stage is when driving becomes affected – many people have cataract surgery when vision falls below or approaches the 6/12 legal level for driving.

The Development of Cataract Surgery

"Cataract" is a Greek term meaning waterfall or flowing down. It was believed that a cataract was an inspissated humor which had seeped from the brain into the space between the cornea and iris. Treatment for over 4,000 years, from antiquity to the mid 18th century, was the operation of "couching", in which the white cataractous lens was displaced inferiorly out of the visual axis.

In 1747 Jacques Daviel made an incision in the inferior cornea and removed a cataract with a needle, starting a new era in eye surgery. He reported 115 cases, with 100 successes, to the Royal Academy of Surgery in 1753. For the next 200 years progress was made in refining techniques for removing the lens, either completely within the lens capsule (intra-capsular cataract extraction), or leaving the posterior lens capsule intact to prevent vitreous coming forward (extra-capsular cataract extraction). Both of these operations are safe and reliable, but need a large incision into the eye – 11mm to 12mm.

A major problem, once the eye has had the lens removed (aphakia), is how to replace the optical focussing power of the lens. Aphakic spectacles (Figure 4a) were the most commonly used method,

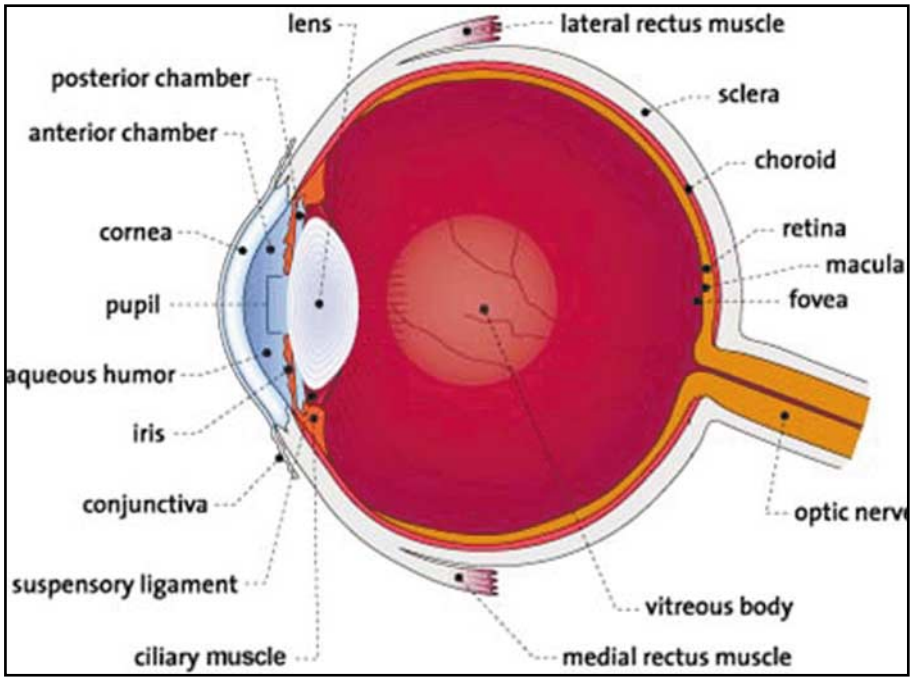


Figure 2

Figure 3

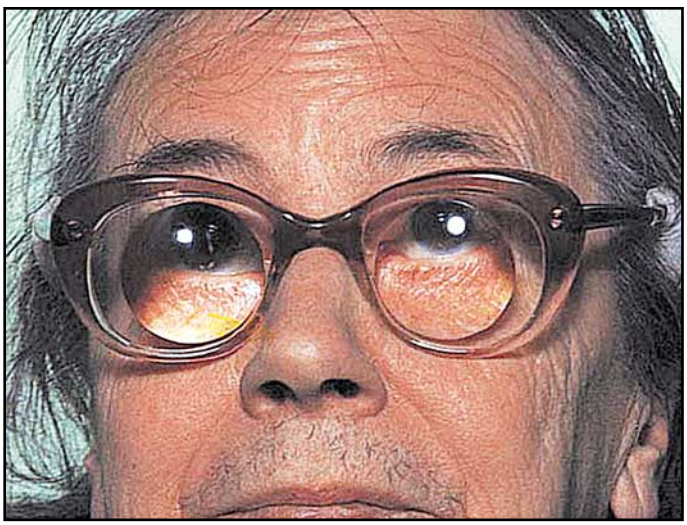


Figure 4a

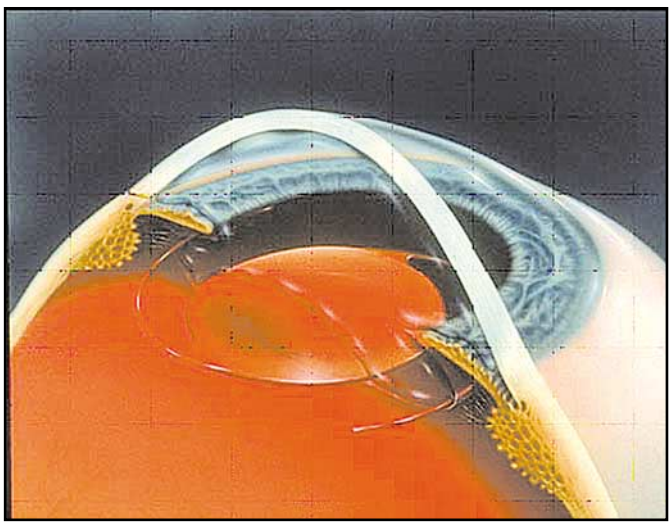


Figure 4b

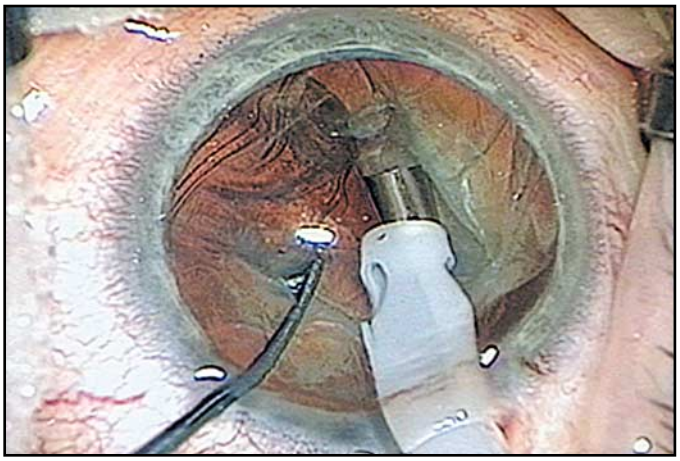


Figure 5a

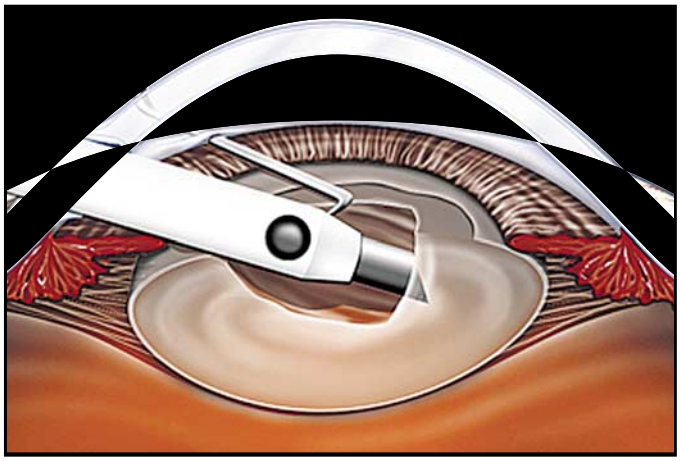


Figure 5b

but they are difficult to get used to, produce high magnification and visual distortion. Contact lenses work well for some people, but the elderly especially have problems in handling and maintaining them. By far the best solution is to replace the lens with an artificial one – an intraocular lens (IOL) – in the same physiological position as the natural lens. (Figure 4b)

There are 2 people who have been most responsible for the modern era of cataract / IOL surgery.

Harold Ridley, an ophthalmologist in the UK, had noted during World War II that intraocular foreign bodies of Plexiglas (small shards from the plastic canopy of the Spitfire fighter) in injured RAF pilots were inert and well tolerated, unlike the numerous other types of intraocular foreign body injuries encountered during wartime. From this he developed the idea of using Plexiglas, which was monomer-free polymethyl-methacrylate (PMMA) as an IOL material. On November 29th, 1949 at St Thomas's Hospital in London he was the first to implant a plastic intraocular lens, made from PMMA. This was highly controversial as many believed that an eye would not tolerate such a foreign body. The eye did in fact tolerate the IOL material well, but the IOL was so heavy (106mg in air) that it sank back into the vitreous.

Complications in the early Ridley series were so common that the procedure was largely abandoned for 20 years. In the early 1970s a new generation of ophthalmologists in Europe and the US developed innovative designs for IOLs in the anterior and posterior chambers, and this, combined with improved surgical techniques and the development of the operating microscope, led to greatly improved surgical results and gradual acceptance of IOLs as the best management of aphakia.

IOLs have gone through many design and material refinements over the years, and their implantation has now become routine. Currently we are using foldable silicone or acrylic IOLs which can be implanted through a 2.8mm incision.

Charles Kelman, a New York based ophthalmologist, in 1967 pioneered the **phacoemulsification** operation. He had been working on ideas to break up the cataractous lens within the eye and aspirate it through a small incision, rather than the large 11mm to 12mm incision needed with conventional lens extraction operations. Large incisions need multiple sutures and prolonged postoperative recovery time. Kelman had tried, without success, various intraocular drills, rotators and vibrators. All damaged the delicate corneal endothelium. While at his dentist, having his teeth cleaned with an ultrasound handpiece, he came upon the idea of using high speed ultrasound to break up the lens within the eye. This is the same principle used today.

The modern phaco handpiece generates ultrasonic vibrations at a frequency of 28 – 40 KHz by means of a piezoelectric crystal enabling fragmentation of the lens nucleus.

The 3 modalities controlled in the handpiece by the phaco machine are: 1. ultrasound power 2. aspiration 3. infusion. Each of these three can be independently controlled by the surgeon with a multifunctional footpiece (all done with 1 foot – the other foot controls the operating microscope focus and zoom during the operation). At all times it is vital that the rate of fluid infusion into the eye is the same as fluid (and lens debris) aspiration out of the eye to maintain a steady intraoperative intraocular pressure while emulsifying the lens. (Figures 5a and b)

Current Status of Cataract Surgery

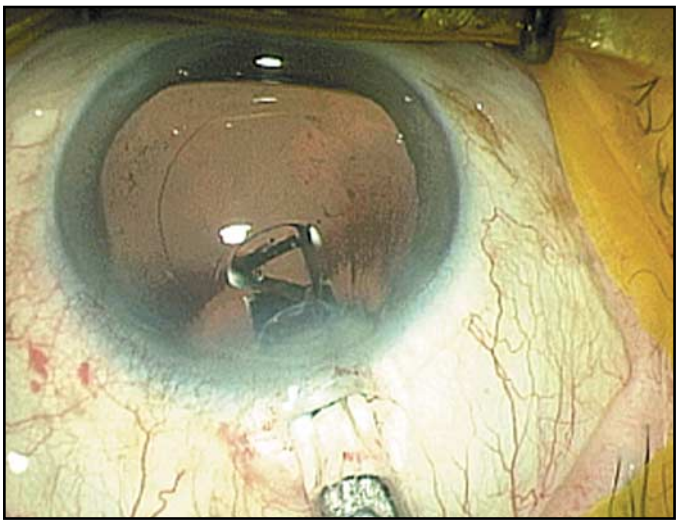
Modern cataract surgery is underpinned by three factors :

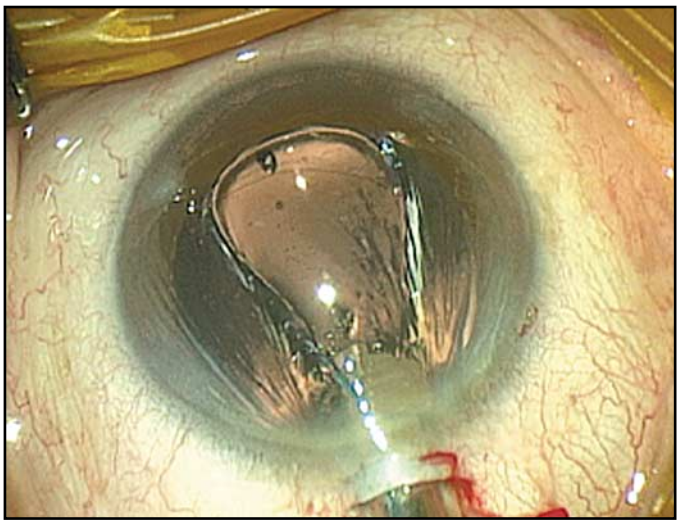
1. **topical anaesthesia**
2. **phacoemulsification surgery technique**
3. **IOL design**

Topical anaesthesia has replaced retrobulbar or peribulbar local anaesthetic injections (or previously general anaesthesia). Anaesthetic injections around or behind the eye run the risk of orbital haemorrhage, globe perforation and optic nerve damage. Topical anaesthesia is safer and more gentle – this involves multiple drops of **Narapin** (Ropivicaine 10%) onto the cornea, started about 30 mins pre-op, supplemented with intravenous **Midazolam** and **Alfentanyl** (short acting sedatives).

The surgery is done using a 2.8mm to 3.0mm incision, usually using the temporal clear cornea approach with an ultrasharp steel or diamond blade. This is an avascular area, and thus, when combined with topical anaesthesia, there is no risk of bleeding at all – patients on Warfarin or other blood thinning agents do not need to stop them.

IOLs have an optical zone of 6mm diameter, and an overall length of 13mm, so to overcome the problem of how to insert such an IOL through a





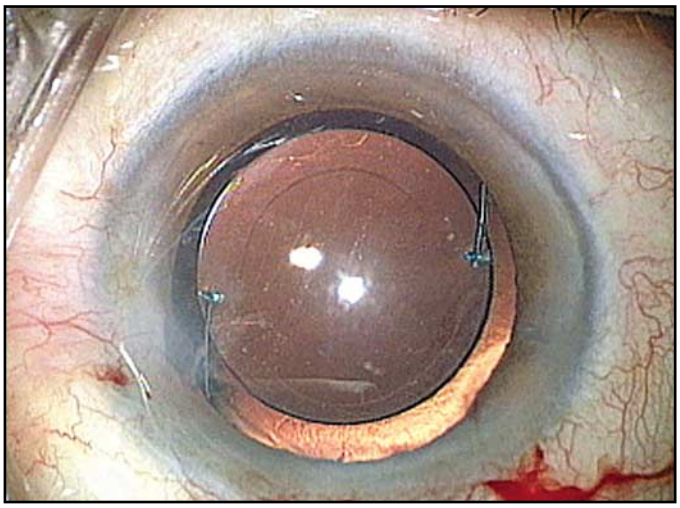


Figure 6a

Figure 6b

Figure 6c

small incision the solution is – to fold the IOL or roll it up in a special inserting cartridge. Previously rigid PMMA was used for IOLs, but now soft silicone or acrylic IOLs are available, allowing insertion through a small incision. As it enters the eye through the cartridge the IOL gently unfolds (Figures 6a-c) The incision is obliquely positioned in the cornea – it is self sealing and no suture is usually needed at all. The IOLs also have an ultraviolet filter to protect the retina from harmful short wavelength UV light, which has been implicated as a contributing factor in age related macular degeneration.

Complications of surgery are uncommon – about 2% of cases. These include:

a) infection – post operative endophthalmitis can be devastating – minimised by pre- and post-op antibiotic drops and meticulous attention to surgical detail

b) posterior capsule tear – if a tear occurs in the posterior lens capsule during the operation vitreous may come forward. A vitrectomy then needs to be done and it may not be possible to implant an IOL as planned

c) post operative cystoid macular oedema – swelling of the macula (usually transient) causing blurring of vision

d) refractive "surprise" – despite the usual pre-op ultrasound measurements and calculations, sometimes the power of the implanted IOL does not give the predicted refractive result. This is now the leading cause in the US of needing to replace an IOL.

Special considerations in cataract surgery

One eyed patient

When the fellow eye is blind or absent (from whatever cause), having cataract surgery does not inherently increase the risks of surgery but should a problem occur, the implications for the patient are far more significant. Often in such cases the patient delays surgery as long as possible – the problem with this is that intraoperative complications are more likely when operating on an advanced cataract.

Other ocular pathology

With co-existent pathology, e.g. glaucoma, macular degeneration, diabetic retinopathy, the visual result from cataract surgery may be compromised.

If a patient also has glaucoma, a **glaucoma** drainage procedure (trabeculectomy) can be combined with the cataract operation. This has the added advantage that the patient may not need to use glaucoma drops in the long term, but the surgical procedure is more complex and prone to complications.

Macular degeneration is common in the elderly. We may elect to give an intravitreal steroid injection (triamcinolone) during the cataract operation to minimise posterior segment inflammation which can accelerate macular degeneration.

Diabetic retinopathy needs to be identified and treated with laser ablation prior to the cataract surgery. If there is active retinopathy at the time of surgery, this will become rapidly worse post operatively.

Frequently asked questions in cataract surgery

Can the cataract return?

No, once it is removed the cataract cannot return.

Does the IOL ever need replacing?

No, the IOL is there for good. It has no moving parts to wear out. Its sole purpose is to remain in position to focus light onto the retina.

Is the cataract removed with laser?

No, the phacoemulsification operation is done with ultrasound. Laser is sometimes needed months or years after the operation to clear posterior capsular fibrosis. This is with a YAG laser, not to be confused with the excimer laser promoted for corneal refractive surgery.

Future developments

Bimanual phaco

In an effort to reduce the wound size even more, bimanual phaco, using a 1.2mm incision, has been developed. This requires different instrumentation and takes longer than standard phaco operations. Currently, the benefits are not all that great, as the wound still needs to be enlarged to insert the IOL, but we may shortly be seeing new forms of IOL which can go through an ultrasmall incision.

Multifocal IOLs

To overcome presbyopia (loss of accommodation with age) a range of multifocal IOLs are available (Figure 7). These can make patients independent of spectacles, but visual problems are common (annoying glare and halo at night, especially with driving) and their use has not been universally accepted.

Refractive Lens Exchange (REFLEX)

With increasing success rates for surgery, many now see cataract surgery as a refractive procedure. Due to our ability to alter patients' refraction by manipulating the IOL power, we can eliminate myopia, hypermetropia, and to a lesser extent astigmatism. Lens based surgery is now a realistic alternative to corneal refractive surgery, especially in the over 40s age group. In other words, rather than waiting for a cataract to develop, it is possible to replace the natural lens with an IOL, mainly for refractive rather than therapeutic indications.

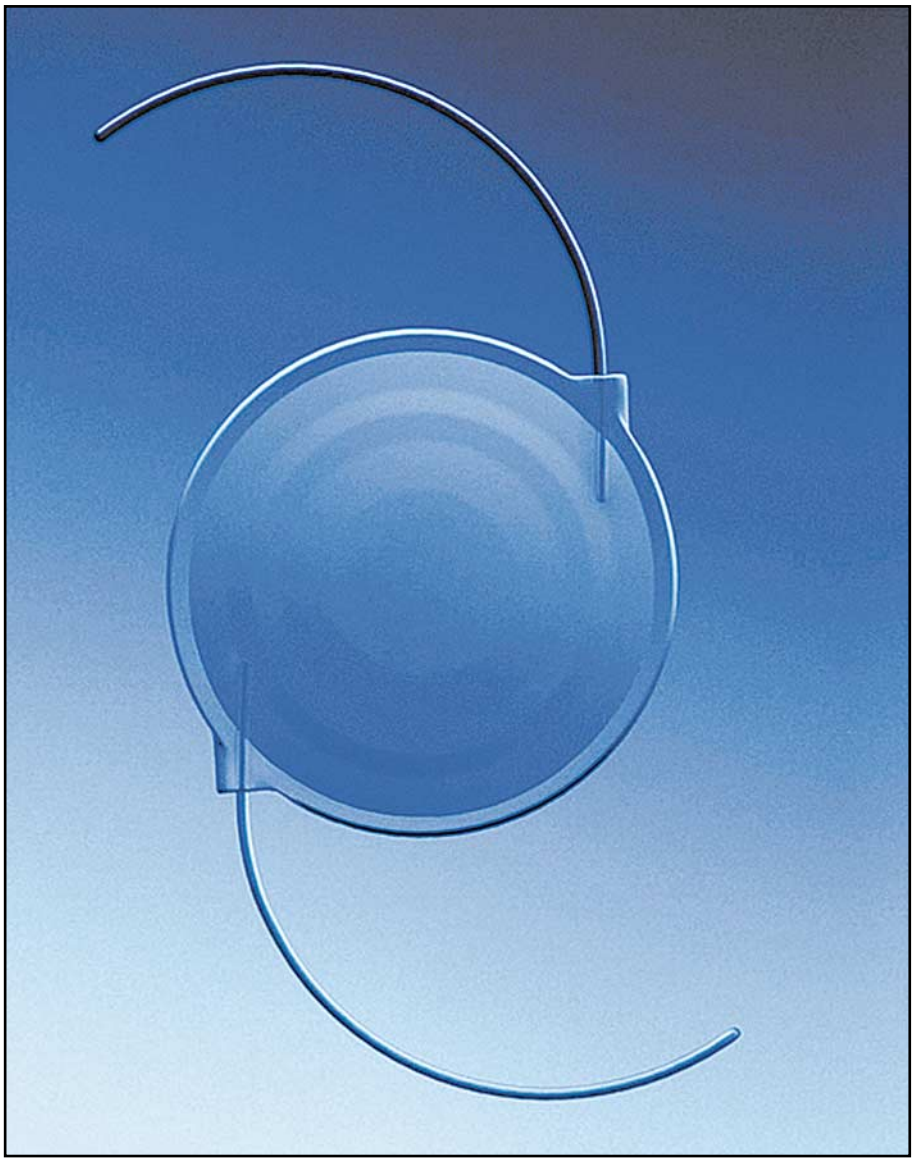
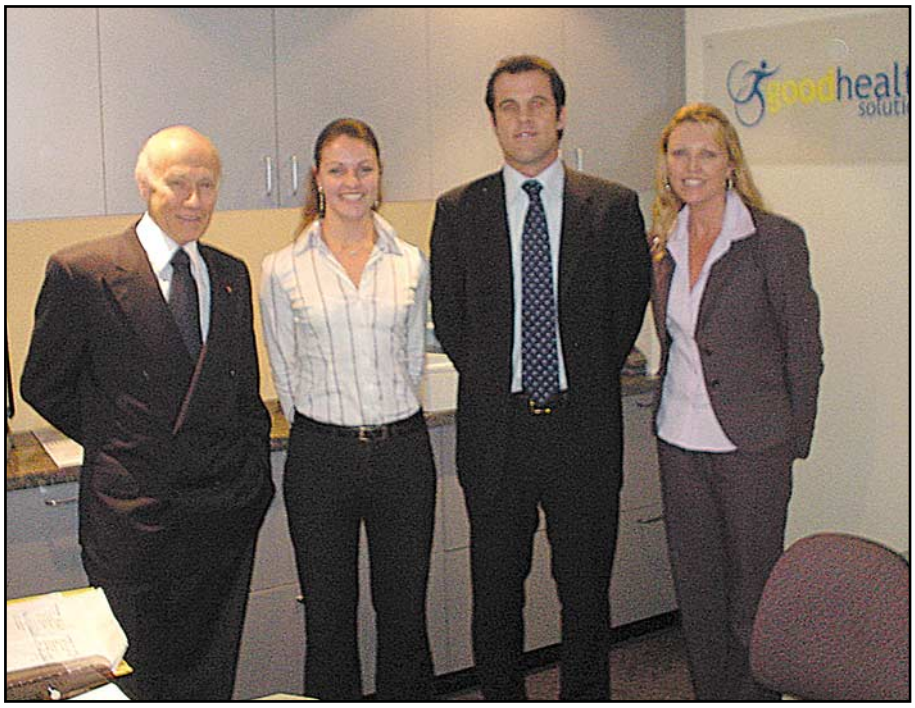


Figure 7

This opens new and exciting surgical possibilities, but also new ethical dilemmas, far beyond anything Dr Green could have anticipated back at the 1905 Academy meeting

Professor Ronald Penny
Dr Peter Slezak

Health and Wellbeing for Corporate: Workplace Health Management



History

In 1991, Peter O'Brien established the Health Assessment Centre at St Vincent's Clinic Sydney and over the years built up a highly respectable corporate and private clientele seeking a high level assessment to cover health and lifestyle risks as well as detecting early disease. In 1999 a second Health Assessment centre was set up at St Vincent's, Melbourne. In 2003, Good Health Solutions, a private company, acquired the two centres appointing Professor Ronald Penny as its Medical Director.

Good Health Solutions however offers a broader approach to workplace health. Good Health Solutions provides an organisation wide health risk assessment and health audit followed by the appropriate health interventions that will lead to improvement in the performance of both individual and organisations by the promotion of healthy lifestyle choices.

This report will focus on the executive and senior management end of the workforce spectrum as assessed at St Vincent's Sydney and Melbourne centres and the recently acquired Health Assessment Centres at 44 Market Street and 1 Martin Place.

Why Health?

Health and disease outcomes are mainly determined by lifestyle with an estimated seventy percent of chronic diseases — heart disease, stroke, diabetes, cancers and high blood pressure — being preventable or deferrable by lifestyle choices. These are themselves influenced by the physical and social environments within which the choices are being made. In addition, the genetic makeup of the individual and the environmental impact from infection, chemical or toxic exposure and injury influence health. Major lifestyle contributors to disease are physical inactivity, poor nutrition, stress, smoking, alcohol excess, sleep disturbances, fatigue and work/life imbalance.

Professor Ronald Penny AO, MD, BS, FRACP, FRCPA
Medical Director, and
Dr Peter Slezak MB, BS, FRACP, MACLM

Physical activity alone will reduce the risk of all causes of disease and mortality. Physical activity, healthy nutrition and optimal body weight can reduce the risk of heart disease, stroke, diabetes and a number of cancers. Physical activity can also reduce depression and anxiety. Stress and certain behavioural patterns particularly time urgency, impatience and hostility can contribute to heart attacks. Healthy diet, avoidance of smoking and excess sun exposure, and physical activity can prevent up to 1/3 of cancers. Lifestyle changes require enduring intervention with educational reinforcement — more than just knowledge.

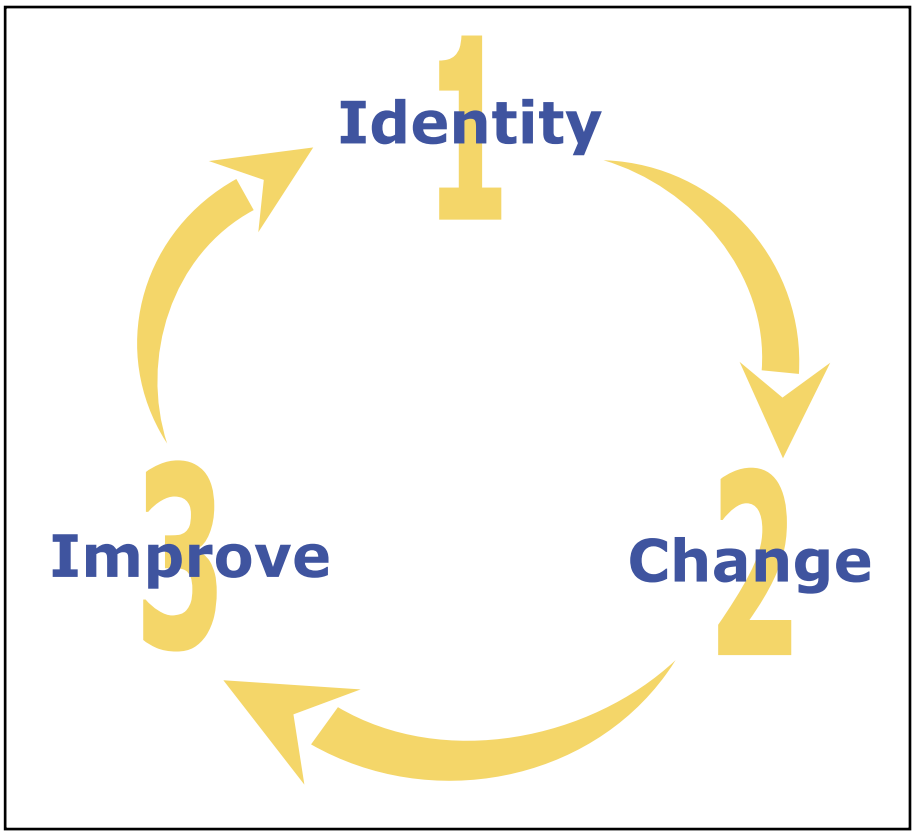
Why Health Risk Assessments?

Health risk assessment provides the early identification of medical conditions or risk factors for future disease, such as high blood pressure, elevated cholesterol, blood sugar or excess weight. The risk assessment identifies which lifestyle behaviours require intervention. Up to 90% of an otherwise healthy population have at least one but usually many more than one significant lifestyle behaviour which will predispose to subsequent ill health, disease or premature death.

Why Workplace Health Management?

With the average employee working 53 hours per week, the majority of our awake hours are spent working. The workforce from senior executives to general staff presents organisations with a high investment and heavy dependence on both the intellectual and working capital of the employees. Poor health reduces longevity at a time at which workforce predictions will require a need for workers to remain healthy to continue to work for a longer period. Poor health contributes to reduced employee productivity by all parameters.

Temporary or permanent loss of employees can have an impact on Clients as well as organisational structure and function. Poor health contributes to reduced productivity through absenteeism, presenteeism (i.e. turning up for work, but not functioning at full capacity), staff turnover and increased risks of errors, accidents, injury and high premiums for workers compensation. The cost to business through loss of productivity attributable to preventable disease in the US is estimated at greater than $500 billion. This US data excludes injury and mistakes related to alcohol, fatigue and mental disturbances, particularly prevalent in shift workers. It also excludes direct health costs influencing the national health bill.



Conversely, studies of the effectiveness of large corporate health and wellness programs have demonstrated positive benefits to the organisation in addition to increased productivity, namely: improved staff morale, positive cultural change and social responsibility of the company which enjoys the role of employer of choice in the relevant sector.

What is Workplace Health Management?

Work health management represents an ongoing program linked to other workplace human resource programs such as occupational health and safety and represents a commitment to a healthier and more productive work force.

An audit (1-Identify) of the health risks of executives, managers and general staff can be undertaken by an assessment which is stratified according to the organisational needs. After the assessment, the individual is provided with a confidential report and the company receives aggregate data on the health risk profile of its employees. This aggregate data provides a needs assessment for organisation-wide health management programs.

Program

An ongoing health and wellness program (2-Change) addressing key risks can be initiated and health risks and outcomes for employees can be tracked against key performance indictors relevant to the company. Studies have shown that these programs need to be ongoing and need to engage senior executives and staff motivationally and champions within the organisation to drive support. Measurable benefits to the employer and employee need to be communicated. Resources for such programs may be provided by the organisation, employee or via an organisation contribution. The improvement measure (3-Improve) at

the conclusion of the first cycle becomes the basis of the ongoing program of continuous improvement and becomes embedded in workplace management.

The Health Assessment Centre at St Vincent's Clinic

Prior to attending the Centre, the Client is requested to complete a detailed health questionnaire online [http://www.goodhealthsolutions.com/survey] such that it is available to the Medical Examiner immediately prior to conducting the Health Assessment. There will be an attachment of the health questionnaire at this point.

The detailed questionnaire seeks important information with respect to lifestyle factors eg: diet, exercise, smoking, alcohol patterns, background health issues, family history and importantly an assessment of stress factors.

Prior to the medical examination, assessment of body habitus, blood pressure, auditory, visual assessment and spirometric assessment of lung function is undertaken by an Exercise Physiologist. The Client's age and gender will thereafter determine the extent of the detailed laboratory evaluation undertaken and importantly the results of the laboratory investigations are generally available at the conclusion of the detailed examination. Additionally, where appropriate, mammography, pap smear and bone densitometry are also performed.

The information on the completed health questionnaire is discussed in detail with the Client, with problem areas having being highlighted.

The next step in the Health Assessment is a detailed, careful clinical examination (which may include pelvic/digital rectal examination). At the conclusion of the clinical examination the Client undertakes a stress test under the supervision of Doctor and Exercise Physiologist (subject to no exclusion criteria).

The Health Assessment pathway includes discussions of various laboratory investigations, particularly with respect to the cardiac risk profile and results of the renal and liver function tests. Where appropriate advice may be given to the Client with respect to seeking the assistance of an Exercise Physiologist, Dietitian and at time seeking the opinion of Specialist Colleagues at St Vincent's Clinic.

Discussion with respect to any significant abnormal laboratory test results and where appropriate, Clients are advised to seek any follow-up care through the Client's local medical practitioner.

The Health Assessment findings, advice with respect to any abnormal clinical/laboratory results together with the laboratory test results are in turn forwarded to the Client within 10-14 days of the Health Assessment.

Development

Over the past two years, Good Health Solutions has expanded significantly in its corporate clientele, including many of the major companies in Australia, through acquisitions of two other providers and affiliations around Australia. Good Health Solutions in all is able to provide services to all levels of employees in capital cities as well as regional and remote sites.

A wide range of interventions are provided including seminars, workshops, print material, electronic based health information and prompts for health information for self help. Harvard University Health service guidebooks provide self directed learning and personal one on one interventions where requested. Good Health Solutions is assisted by a health advisory board of nationally recognised authorities and participates in ongoing quality management aiming to provide the highest quality evidence based service by doctors and other health workers.

Benefits for your Organisation

The following organisational wide benefits are potential outcomes of the implementation of a workplace health management program:

- Healthier and more active employees;
- Higher productivity;
- Less absenteeism;
- Fewer medical and workers compensation claims;
- Improved morale;
- Enhanced employee recruitment and retention ("Employer of Choice"); and
- Enhanced company profile.

Benefits for your Employees

The employees who participate in the program will benefit in a number of ways including:

- Improved health awareness including knowledge of specific, individual health risks;
- Increased education on optimal nutrition and wellbeing;
- Improved morale;
- Greater job satisfaction;
- Enhanced self-esteem and confidence; and
- Better health, improved quality of life, more energy.

Conclusion

Within a few years Good Health Solutions has become one of Australia's leading providers of both Executive Health Assessment and Workplace Health Management programs focusing on the maximising health and wellbeing status of employees. Good Health Solutions pays tribute to the earlier work of St Vincent's Health Assessment Centre, where the emphasis was on Executives, but is now proud of its current status and range of corporate clients, but not losing sight of the loyal private individuals who have used the service for many years.

Dr Reginald V.N. Lord

Gastroesophageal Reflux Disease

Introduction

Several developments for investigating gastroesophageal reflux disease (GORD) have been introduced on the St. Vincent's campus this year. These include a permanent onsite centre for oesophageal manometry, the Bravo catheter-free oesophageal pH monitoring system, and video-oesophagography. St. Vincent's Clinic is the only centre in NSW to offer the Bravo catheter-free pH test. These recent developments have prompted this review of the current approach to the evaluation of GORD. An improved understanding of the role of surgical therapy for GORD has also been achieved recently. This is reviewed in the second part of this article.

Gastroesophagael reflux disease is common in Western societies. Approximately 10 per cent of adults experiencing heartburn daily, and more than one third have occasional heartburn. This high prevalence could suggest that reflux disease is a minor ailment, but patients with GORD have a significantly reduced quality of life. One study reported that patients with untreated GORD had worse quality of life scores than patients with mild heart failure. Furthermore, because longstanding severe GORD is the principal risk factor for the development of Barrett's oesophagus, patients with GORD are at increased risk for developing adenocarcinoma of the oesophagus or gastroesophageal junction.[1] The incidence of oesophageal adeno-carcinoma is rising faster than that of any other cancer in many countries, including Australia.[2]

Dr Reginald V.N. Lord MD, FRACS
Upper Gastrointestinal Surgeon
St Vincent's Clinic

Symptoms of Reflux Disease

Reflux of small amounts of gastric juice into the oesophagus is a normal physiological event. GORD occurs when this reflux becomes excessive. This may be manifested by typical or atypical symptoms, endoscopic or histologic oesophagitis, or by measurement of increased oesophageal acid exposure on prolonged ambulatory pH monitoring. Diagnostic evaluation is based upon taking a detailed history. Physical examination may show dental erosions and other pathology but is usually unhelpful otherwise.

The principal typical symptom of GORD is heartburn (pyrosis), which is a retrosternal burning discomfort or pain. Heartburn may be precipitated by bending over or lying flat, especially if the lower oesophageal sphincter (LOS) is mechanically defective. Regurgitation of either gastric juice or food is another typical symptom of GORD. Acid regurgitation is typically sudden and effortless, may be associated with belching, and tastes sour or bitter ("acid brash"). Forceful regurgitation, in contrast, usually consists of bland tasting food which has not entered the stomach, and is typical of an oesophageal body motor disorder or oesophageal obstruction.

Both heartburn and regurgitation are more common within the first hour after meals. Refluxogenic stimuli include large, fatty, or spicy meals, chocolate, onions, peppermint, garlic, nicotine, fruit juices, and drinks that are carbonated or contain alcohol or caffeine. Rapid production of saliva in response to a reflux episode may be perceived as a volume of slightly salty or tasteless fluid in the mouth, a symptom known as "waterbrash". Reflux dyspareunia, or heartburn and regurgitation during intercourse, is not uncommon in females with GORD. In children, the adoption of unusual postures can be a symptom of reflux and is referred to as Sandifer's syndrome.

Dysphagia is a typical symptom of advanced GORD. It can be caused by tissue oedema associated with acute severe oesophagitis, a distal oesophageal stricture, or by loss of oesophageal compliance or motility due to chronic inflammatory changes in the oesophageal wall.[3] Dysphagia may also be due to the presence of a large (>5 cm) hiatus hernia. Malignancy or a named oesophageal body motility disorder needs to be excluded in patients with dysphagia, even if a diagnosis of GORD is likely. Dysphagia due to GORD usually develops slowly, and patients may unconsciously adjust their eating habits to account for the difficulty with swallowing. Consequently, it is important to take a detailed swallowing history in patients with suspected GORD, questioning them as to whether they cut food into small pieces, always finish eating after others, or avoid eating in company. In general, patients with obstructive dysphagia localise the site of obstruction either at, or proximal to, the anatomical level of the obstruction. Pain on swallowing (odynophagia) occurs in up to 50 per cent of patients with reflux oesophagitis. Many patients initially complain of "indigestion", in which case further enquiry is needed to determine more precisely the specific symptom or symptoms experienced.

Atypical and extra-oesophageal symptoms of GORD include chest pain, epigastric pain, bloating, and pulmonary symptoms. These can be the only symptoms of GORD. Non-cardiac chest pain is caused by GORD in up to half of those with normal coronary angiography. The pain can be induced by exercise and can masquerade as angina pectoris, although the lack of a relationship to exercise helps differentiate most cases of reflux-induced chest pain from true angina.

Airway symptoms of GORD include chronic hoarseness (the Cherry-Donner syndrome), chronic cough, and symptoms of asthma such as wheezing and shortness of breath. Episodic or chronic aspiration can cause pneumonia, lung abscess, and interstitial pulmonary fibrosis. GORD is the underlying cause of chronic cough in 6-10% of patients with this symptom. Asthma-like symptoms are more likely to be caused by GORD in patients with adult onset, non-allergic asthma, and in patients who have typical symptoms of GORD as well as asthma symptoms. At least 50 per cent of asthmatics who have typical symptoms of GORD have abnormal oesophageal acid exposure on prolonged pH monitoring. Reflux is secondary to asthma in many of these patients because the intrathoracic pressure alterations caused by the increased work of breathing increase the peritoneo-pleural pressure gradient.

Patients who reflux into the proximal oesophagus above the level of the upper oesophageal sphincter (laryngo-pharyngeal reflux) may have a hoarse voice, voice fatigue, chronic throat clearing, dental erosions, and reflux laryngitis. Laryngeal pathology in these patients commonly includes erythema and oedema of the vocal cords, but ulceration of the cords and arytenoids, vocal nodules, granulomas, and even carcinoma may result from laryngopharyngeal reflux. Direct reflux of gastric fluid into the lungs is not necessary for the development of GORD-related airway symptoms, because the symptoms may be provoked by distal oesophageal acid exposure via an oesophago-tracheobronchial reflex pathway. GORD is a cause of cryptogenic pulmonary fibrosis and patients with this diagnosis should undergo oesophageal pH monitoring, especially if they have had, or are being considered for, lung transplantation.

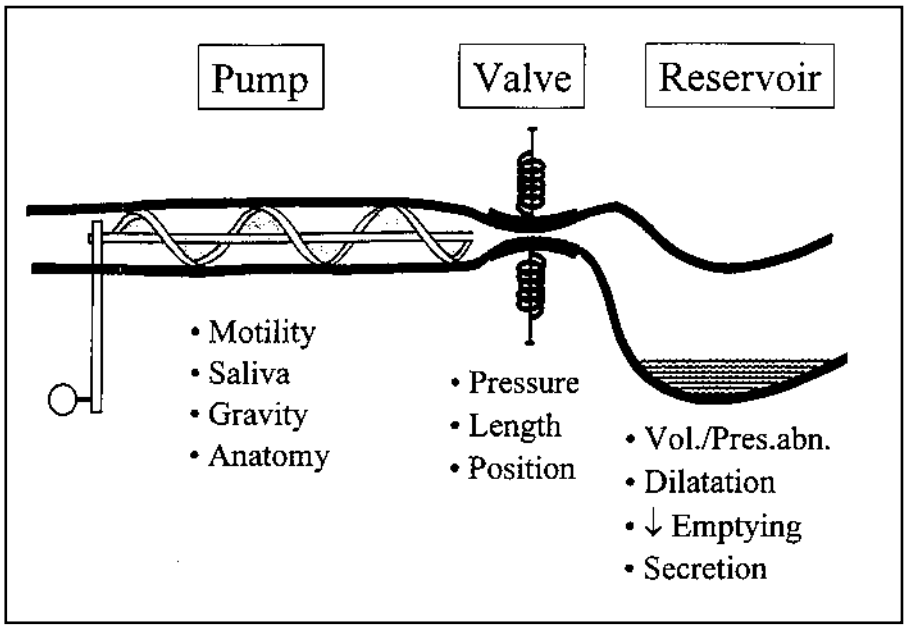


Figure 1. *Mechanical model of the antireflux mechanisms, showing the oesophageal body acting as a pump, the lower oesophageal sphincter as a valve, and the stomach as a reservoir (from Ref. 6).*

Airway symptoms due to GORD often occur at night, when they can be very distressing for the sufferer. Nocturnal reflux, with choking, coughing, shortness of breath and wheezing, will often wake the patient from sleep. In the morning, the patient may complain of a foul taste in the mouth, halitosis, a hoarse voice, or tiredness.

PATHOGENESIS

The aetiology of GORD involves epidemiological, lifestyle, physiological, and genetic factors. One study investigated 1,147 patients with symptoms suggestive of reflux disease who underwent distal oesophageal 24 hour pH monitoring and completed a detailed questionnaire.[4] Significant independent risk factors for GORD were male sex, older age, white Caucasian ethnicity, higher body mass index, and tobacco smoking. Alcohol use was a risk factor in those with an average consumption of more than 30g per day. The most significant risk factors were physiological factors indicating a structurally defective lower oesophageal sphincter (LOS), as will be discussed. There was also a significant inverse association between GORD and the presence of gastric Helicobacter pylori infection, indicating that colonisation with this organism may have a protective effect for the development of GORD. The mechanism by which H pylori infection has this effect is unclear, but may involve a neutralising effect on gastric acidity. A study from St. Vincent's Hospital similarly found an inverse relationship between H pylori colonisation and the presence of either Barrett's oesophagus or adeno-carcinoma,[5] but the relationship between H pylori and GORD remains controversial.

The normal mechanisms that protect the oesophagus from excessive exposure to injurious gastric contents are illustrated schematically in **Figure 1**.[6] As shown, the antireflux mechanism can be classified as having *pump*, *valve*, and *reservoir* components. GORD results from a defect in one or more of these components, with the risk of complications progressively increasing with the loss of each additional component.

The most important antireflux component is the valve, or lower oesophageal sphincter (LOS). The LOS can be identified manometrically as a 2-4 cm asymmetric zone of high pressure in the distal oesophagus. The common event for virtually all reflux episodes, whether physiologic or pathologic, is the loss of the normal resistance imposed by the LOS to the flow of gastric juice from an environment of higher pressure, the stomach, to an environment of lower pressure, the oesophagus. In normal subjects or patients with early disease this loss is transient. In patients with severe disease this loss is usually permanent and is manifested by a reduced or non-existent high pressure zone.

The pinchcock action of the crural diaphragm, which closes the oesophageal hiatus during short periods of diaphragmatic contraction and raised intra-abdominal pressure, such as occurs during straining or coughing, adds to the effectiveness of the gastroesophageal antireflux barrier. The presence of a hiatus hernia impairs the sphincter function of the crural diaphragm and the additive pressure effect created by the superimposed LOS and crural antireflux components is lost in patients with larger hernias, in whom the LOS and crura are separated.

The pump antireflux mechanism includes the peristaltic function of the oesophageal body, the effect of gravity in the upright position, and the neutralising effect of saliva. These are important for clearance of refluxed material from the oesophagus. Primary peristaltic waves are responsible for volume clearance of refluxed acid. Any acid that remains in the oesophagus after volume clearance is neutralised by the alkaline saliva. Patients with xerostomia, impaired oesophageal peristalsis, or reflux during sleep, when primary peristaltic waves are infrequent, are more likely to have mucosal injury from GORD because of defective pump function.

Defective organisation of the contraction waves impairs oesophageal clearance. Abnormal waveforms can be dropped (incomplete), interrupted (skipped segments), or rapid (appearing as a simultaneous contraction throughout the oesophageal body). Clearance can also be impaired by the presence of a hiatus hernia due to the loss of abdominal anchoring of the oesophageal body.

Abnormalities of the gastric reservoir that predispose to GORD include gastric distension, impaired gastric emptying, and gastric acid hypersecretion. Approximately 40 per cent of patients with GORD have delayed gastric emptying. Gastric distension can be caused by ingestion of excessive quantities of air or of fatty and fried foods that delay gastric emptying. Gastric distension causes transient LOS relaxation, resulting in reflux episodes.

Diagnostic Evaluation

Important components for the diagnosis of GORD include the patient's history, endoscopic findings, radiological abnormalities, and the measurement of increased oesophageal exposure to gastric acid on pH monitoring. These components are complementary, and the presence of more than one is usually necessary for a confident diagnosis. The use of symptoms alone, even if they are predominantly typical GORD symptoms, will result in misdiagnosis in some patients. Prior to considering aggressive medical or surgical therapy, it is important to establish that GORD is indeed the cause of the patient's complaints. Investigations are important before antireflux surgery to identify motility disorders, oesophageal shortening, or a large hiatal hernia, as these factors may influence the operative approach.

GORD can reliably be diagnosed if a patient has typical symptoms and at least one piece of objective evidence of reflux, such as an abnormal oesophageal acid exposure on prolonged pH monitoring or visible oesophagitis. A biopsy showing inflammatory cells infiltrating the mucosa on histology provides weaker objective evidence. For patients with atypical symptoms, the clinician should be more conservative, requiring two pieces of objective evidence to establish the diagnosis of GORD. In patients with atypical respiratory symptoms, endoscopic laryngitis can be counted as one piece of evidence.

Investigations

i. Endoscopy

The indications for performing endoscopy are controversial. One approach is to perform endoscopy with mucosal biopsy in patients with the following conditions: (1) a history of heartburn or regurgitation lasting longer than 6 months, (2) atypical symptoms, (3) a poor response to medical treatment, and (4) the presence of "warning symptoms" such as dysphagia, odynophagia, bleeding, weight loss, respiratory symptoms, or chest pain. Endoscopy is the procedure of choice for diagnosing reflux oesophagitis. Reflux oesophagitis may be present histopathologically even if the mucosa appears normal endoscopically.

It must be noted that most patients in the community with reflux disease have a macroscopically normal oesophageal mucosa. These patients have non-erosive reflux disease (NERD) and may be more difficult to treat medically than those with oesophagitis.

Endoscopy is required to diagnose Barrett's oesophagus, in which the normal squamous epithelium of the distal oesophagus is replaced with columnar epithelium in response to chronic reflux. The current definition of Barrett's oesophagus requires the presence of any length of macroscopically visible columnar mucosa, along with microscopic evidence of intestinal metaplasia with goblet cells.

ii. Barium swallow

Although not a standard primary study for GORD, a barium swallow examination may be helpful for investigating patients with known or suspected GORD, especially if operation is planned. A barium study provides information about the handling of liquid and solid boluses and about the presence and reducibility of a hiatus hernia. This information is often not gained from the other tests. More information is obtained if the study is video-recorded ("video-oesophagram") than if only a stationary plain film record is obtained. A hiatus hernia can often only be seen in the prone position. The presence of a fixed non-reducible hernia in both the prone and upright positions can be a sign of oesophageal shortening. In patients who present with dysphagia, a contrast study provides an important "road map" with information about the site and severity of any strictures, diverticula, or tumours that may be present. The barium study also provides information about gastric emptying. Absent antropyloric waves in the stomach with markedly delayed gastric emptying suggests a diagnosis of gastric atony. If the barium swallow study is suggestive of a gastric motility problem, gastric emptying can be further assessed by stationary or ambulatory radionuclide studies.

iii. Oesophageal manometry

Oesophageal manometry is performed in patients with suspected GORD to assess the structural competence of the LOS, to identify oesophageal body motility disorders, and to accurately locate the upper border of the LOS for positioning the pH electrode for pH monitoring.

The resistance of the LOS to the flow of gastric juice into the oesophagus is a function of both its pressure and the

length over which that pressure is exerted. The resting pressure, the overall sphincter length, and the intra-abdominal sphincter length are the three manometric characteristics of the LOS that maintain its mechanical function as an antireflux barrier. A structurally defective LOS is usually associated with oesophageal mucosal injury, which indicates that lifelong therapy will be necessary to control the patient's symptoms.

The second part of the manometry examination is the assessment of oesophageal body function, the most important component of the pump antireflux mechanism. The measured features of individual contractions are the amplitude, duration, propagation speed, and morphology. Non-transmitted, interrupted, spontaneous, and simultaneous waves are also noted. The finding of a named oesophageal body motility disorder suggests that this is the primary cause of the patient's symptoms, but non-specific abnormalities, such as distal oesophageal hypocontractility, may result from longstanding GORD. In these patients, recovery of some body contractility may occur after abolition of ongoing reflux and healing of oesophagitis. If achalasia or scleroderma are found on manometry, an antireflux procedure, if indicated, should be a partial fundoplication type to avoid adding too much outflow resistance to an already failed oesophageal body. Failure to diagnose achalasia in a patient thought to have reflux disease is disastrous if fundoplication is performed without myotomy.

iv. Ambulatory oesophageal pH study

The gold standard test for the diagnosis of GORD is prolonged ambulatory oesophageal pH monitoring, which measures the amount and duration of acid exposure in the distal, and sometimes proximal, oesophagus. Prolonged pH monitoring may also be used to provide an objective assessment of the effectiveness of treatment. In this role, it is sometimes performed in patients while they are taking acid suppressant medications. An important feature of the test is that patients keep a diary of symptoms experienced during the monitored period. This allows the patient's symptoms to be correlated with reflux events. This correlation can be summarised as a Symptom Index.

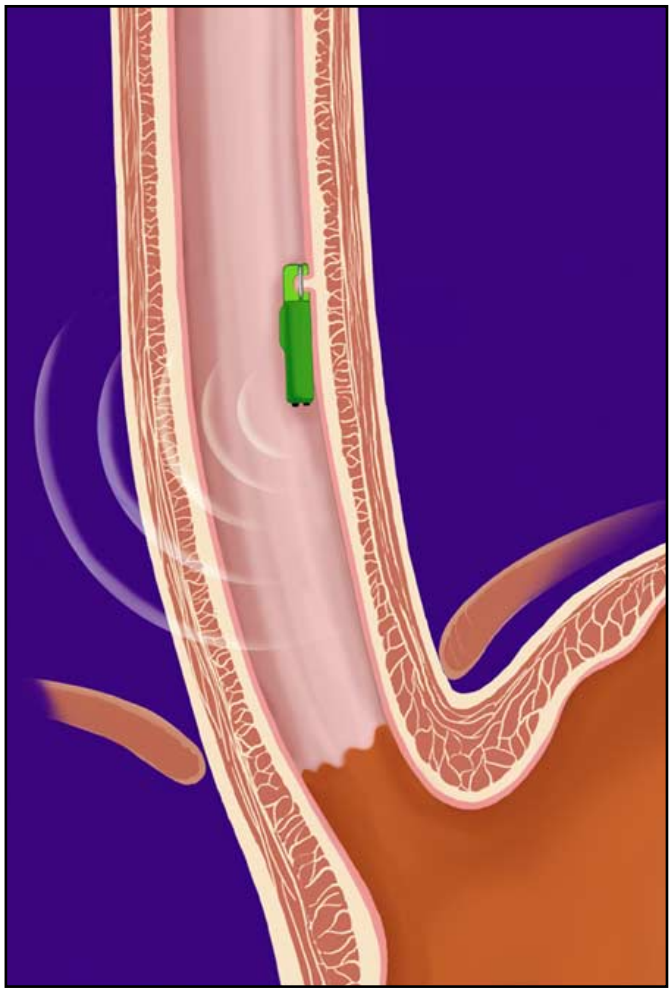


Figure 2. *Schematic figure showing the Bravo capsule attached to the oesophageal mucosa. The probe transmits pH data to a pager-sized receiver worn on the belt or waistband.*

A false negative test may be caused by patients limiting their food intake and activity during the study, partly as a result of the discomfort caused by the standard pH test method, which requires patients to have a transnasal pH catheter for the 24 hour duration of the study. Some patients find that having the catheter is uncomfortable, embarrassing, and interferes with their normal daily activities including eating, potentially resulting in limited reflux during the study period. For these reasons, the Bravo catheter-free pH probe system has been introduced at St. Vincent's Clinic (Figure 2). This new system allows patients to enjoy their normal diet and activities without the discomfort and embarrassment of a catheter.

The Bravo system uses a miniature pH recording capsule that is attached to the lining of the oesophagus under sedation. The capsule transmits pH data to a receiver worn on the belt or waistband like a pager or mobile phone. Patients press a button on the receiver when they have heartburn or other symptoms and they record the times of meals, sleep, and other events in a diary. Unlike the 24 hour catheter study, the catheter-free method collects pH data for 48 hours. Somewhat surprisingly, the acid reflux can be significantly higher in the second 24 hour period than the first, suggesting that patients become less inhibited and conscious of the probe during the latter half of the study.

Dual pH probe catheters, with a proximal probe 15 cm above the distal probe, are used to investigate patients with respiratory or laryngeal symptoms. In normal individuals, reflux episodes causing a fall to below pH 4 in the proximal probe are rare, but are commonly detected in patients with airway disease due to GORD. The finding of a normal amount of proximal acid exposure does not exclude the possibility that GORD is the cause of a patient's respiratory symptoms because airway symptoms such as cough and wheezing may be triggered, via a reflex mechanism, by reflux of acid into the distal oesophagus.

Treatment

Most patients with mild symptoms have either no treatment or self-medicate with over-the-counter drugs

such as antacids, whereas patients with more severe or persistent symptoms seek medical attention. Lifestyle modifications to reduce reflux include elevation of the head of the bed, weight loss, restriction of alcohol, caffeine, fatty and fried foods, avoidance of large meals and meals late at night, and the elimination of tobacco smoking. Lifestyle modifications receive little emphasis now that potent alternative treatments for GORD are available, but they remain an important part of treatment. For many patients with mild disease, a two to three month course of antacids, combined with these lifestyle modifications, will result in adequate symptom relief.

Medical therapy

Patients with persistent symptoms will usually be treated initially with medical therapy. The aim of medical therapy is to reduce the acidity of the refluxed gastric juice. Histamine H2 receptor antagonists are less effective in relieving symptoms and healing oesophagitis than proton pump inhibitors (PPIs), which are the mainstay of current medical treatment. Standard dose regimens of PPIs can reduce gastric acid production by up to 90 per cent, and double dose regimens can reduce acid output by more than 95 per cent. These dosages will heal oesophagitis in the great majority of patients. Severe oesophagitis may be resistant to conventional dosage regimens, and in these patients long-term studies have shown that dose escalation is often needed to maintain healing.

PPIs relieve heartburn in most patients, but they are less effective for relieving regurgitation or pulmonary symptoms. Relief of heartburn does not mean that reflux has been adequately controlled. Prolonged oesophageal pH studies have demonstrated that even in patients taking high doses of proton pump inhibitors, nocturnal gastric acid breakthrough occurs and commonly results in abnormal oesophageal acid exposure. Patients who become asymptomatic often discontinue medications or take medications only when symptoms return, thus allowing ongoing reflux and mucosal damage to occur.

The aim of promotility agents is to increase LOS tone, increase oesophageal body peristalsis, and promote gastric emptying. These drugs have a beneficial effect in some patients, especially those with mild disease. Cisapride is used only infrequently because of its cardiotoxicity, however, and metoclopramide use is limited by its central nervous system side effects. Other promotility agents, such as domperidone, bethanecol, and erythromycin, have been disappointingly ineffective.

Unfortunately, within six months of discontinuation of any form of medical therapy for GORD, 80 per cent of patients will have a recurrence of symptoms. Most patients with GORD will thus require long-term, and perhaps life-long, proton pump inhibitor therapy.

Surgical therapy

The aim of surgical therapy is to stop the increased oesophageal exposure to gastric juice, and as a consequence to relieve the symptoms of GORD, heal oesophagitis, and prevent the development of complications. Properly performed antireflux surgery is a maintenance option for the patient with well-documented GORD who will otherwise require life-long medication use. All patients with objectively proven GORD should be informed that antireflux surgery is a valid alternative to pharmacologic therapy. If patients are informed in this way about surgical treatment, many will prefer this option to medication use. Patients' preference for operative therapy has significantly increased as a result of the development of laparoscopic antireflux surgery. Some patients also choose surgery because they wish to live without the anxiety and inconvenience associated with constant observance of dietary, alcohol, and other lifestyle restrictions.

Indications for surgery

The indications for surgical therapy for GORD have widened recently as a result of a better understanding of the pathogenesis of the disease, clarification of risk factors for disease progression despite medical therapy, and the widespread acceptance that laparoscopic antireflux surgery provides equivalent results to open surgery, with significantly less morbidity. Findings that encourage consideration of operative treatment are the presence of an incompetent sphincter, a large hiatus hernia, severe symptoms other than heartburn, for example regurgitation, and breakthrough of symptoms while on medical therapy. Patients with oesophagitis or Barrett's oesophagus will require life-long medication use and should be considered for surgical therapy.[7] A promising therapy for those with Barrett's with low grade dysplasia is endoscopic ablation of the Barrett's segment followed by abolition of reflux by laparoscopic antireflux surgery.[8]

A greater understanding of the role of surgery is reflected in the following three corrections of previous misunderstandings:

(1) It was formerly thought that antireflux surgery was only beneficial for patients with a structurally defective sphincter, but it is now known that antireflux surgery will also prevent reflux in patients with a structurally normal LOS. The mechanism for this effect is that surgery reduces reflux episodes caused by either transient lower oesophageal sphincter relaxations or transient loss of the high pressure zone due to shortening of the LOS with gastric distension. The presence of a structurally defective sphincter remains a relative indication, however, for surgical therapy.

(2) It was also formerly believed that surgical treatment should only be considered if oesophagitis was present. It is now recognised that most patients with GORD in the community have non-erosive reflux disease or NERD. These patients are candidates for operation if they would otherwise require long-term medical therapy. In fact, several studies indicate that medical therapy is less effective in these patients compared to those with erosive disease.

(3) It was also formerly thought that surgery should be reserved for patients who receive little or no benefit from acid suppressant drugs. It is now evident that these patients are more likely not to have GORD, and are not good candidates for antireflux surgery unless the diagnosis of GORD is definite.[9] A good response to medical therapy identifies patients who are likely to have a good result with surgery. Other factors that predict the likelihood of a successful outcome after antireflux surgery are the presence of typical symptoms and an abnormal composite score or per cent time the pH is less than 4 on 24 hour pH

testing. Patients with atypical symptoms who have a good response to acid suppression therapy are also good candidates for surgery.

Successful antireflux surgery prevents reflux of gastric juice into the oesophagus but preserves the patient's ability to swallow normally. This can be achieved if several principles are adhered to. First, the operation should restore the pressure, the overall length, and the length exposed to abdominal pressure, of the lower oesophageal high pressure zone to normal levels. This augments the resistance to reflux in patients who had a defective LOS preoperatively and prevents sphincter relaxation. Second, the operation should correct a hiatus hernia if present and restore the normal geometry of the gastro-oesophageal junction, with a normal angle of His and at least 1.5 cm of abdominal sphincter length. This maintains competency of the antireflux barrier during periods of increased intra-abdominal pressure. Third, to avoid troubling, long-term dysphagia, the fundoplication should not be made too tight. This can be achieved by constructing the fundoplication over a 60 French bougie, by using both the anterior and posterior fundic walls, and by ensuring that the fundoplication is no longer than 2 cm, is not twisted, and is not positioned below the gastro-oesophageal junction ie. around the stomach (**Figure 3**). The latter is likely to occur if the oesophagus has been foreshortened by disease. Improper placement of the fundoplication below the gastro-oesophageal junction will interfere with vagally-mediated relaxation of the sphincter on swallowing, resulting in prolonged postoperative dysphagia. Postoperative dysphagia has been associated with significant impairment of relaxation, and is reflected by elevation of the residual relaxation pressure. Dysphagia may also result if the resting pressure of the LOS is too high, indicating that the fundoplication was constructed too tight. A fundoplication that is too loose, on the other hand, can result in continued reflux.

Numerous studies have shown that properly performed antireflux surgery provides safe, effective, long-term control of reflux symptoms, with improvements in quality of life, in 90% or more of patients.8 Although it has been shown that many patients remain on acid suppressant medications after antireflux surgery,[10] most of these patients do not have GORD and do not need these medications.[11,12]

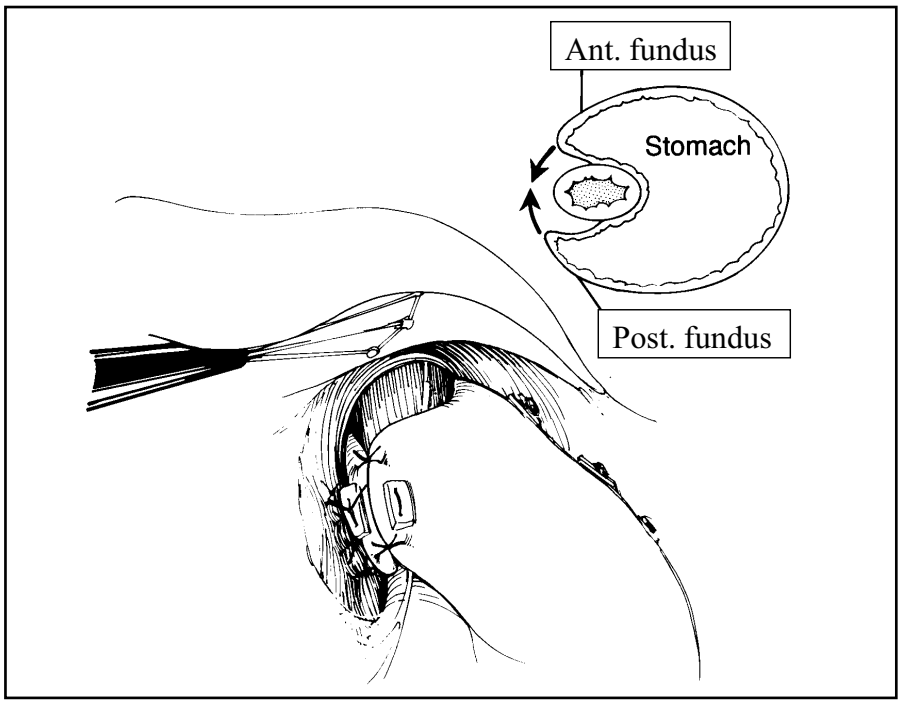


Figure 3. *Schematic appearance of the laparoscopic Nissen (circumferential) fundoplication showing the proper orientation of the anterior and posterior lips of the wrap (from Refs 6 & 7).*

A suggested approach to the management of patients with significant GORD symptoms is to start with a 4 week trial of lifestyle modifications and empirical symptomatic treatment with a PPI. The traditional step-up approach, starting with antacids and progressing to histamine H2 receptor antagonists and then PPIs as needed, remains appropriate for patients with mild symptoms. Patients who have complete relief of symptoms with these measures, with no return of symptoms after cessation of the medications, need no further investigation or treatment. Failure to control symptoms, or return of symptoms after medication cessation, suggests that either the diagnosis is incorrect or that the patient has more severe disease requiring maintenance therapy. Endoscopic examination, ambulatory pH monitoring, and oesophageal manometry studies may then be indicated.

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Hyperuricaemia: Not Just a Matter of Crystals

Introduction

Gout and its co-morbidities are increasingly important public health concerns. The public health implications of hyperuricaemia without crystal complications in our obese populations may prove to be a major issue. Hyperuricaemia and gout should be considered as a component of the obesity/metabolic syndrome, Type II diabetes, and hypertension epidemic that has been occurring worldwide.

In this narrative review, after brief summary of the biochemistry of uric acid, we bring together 3 strands of recent developments in the understanding of hyperuricaemia, its consequences and management. The first is the Health Professionals Follow-up Study, a series of publications led by Hyon Choi arising out of a long-term prospective cohort study of risk factors for gout. While the primary outcome measure in these studies was incident gout, and the correlation between gout and hyperuricaemia is at best approximate, the identified risk factors predominantly influence hyperuricaemia. These data provide important guidance for the prevention of hyperuricaemia and its crystal complications of gout and urolithiasis. The second strand is the increasing evidence especially by Richard Johnson and co-workers, in support of the hypothesis that hyperuricaemia has a pathogenetic role in cardiovascular and renal disease. The third strand is the emergence of new antihyperuricaemic drugs.

Uric acid metabolism in men and animals is shown in Figure 1. Intracellular production of uric acid results from degradation of purines derived from the diet and from nucleic acid metabolism. The mechanism by which poorly soluble intracellular urate enters the circulation requires to be adequately clarified. The excretion of uric acid occurs principally (two thirds) by the kidneys. There is a complex bi-directional (reabsorption and secretion) transport mechanism across renal tubular cells. This is mediated by an urate/anion exchanger and a voltage-sensitive urate channel. The reabsorption of uric acid by the proximal convoluted tubules contributes to the balance of urate in the circulation, which is maintained in a concentration higher than other animals (primates also have relatively high urate). One third of the uric acid is eliminated via the

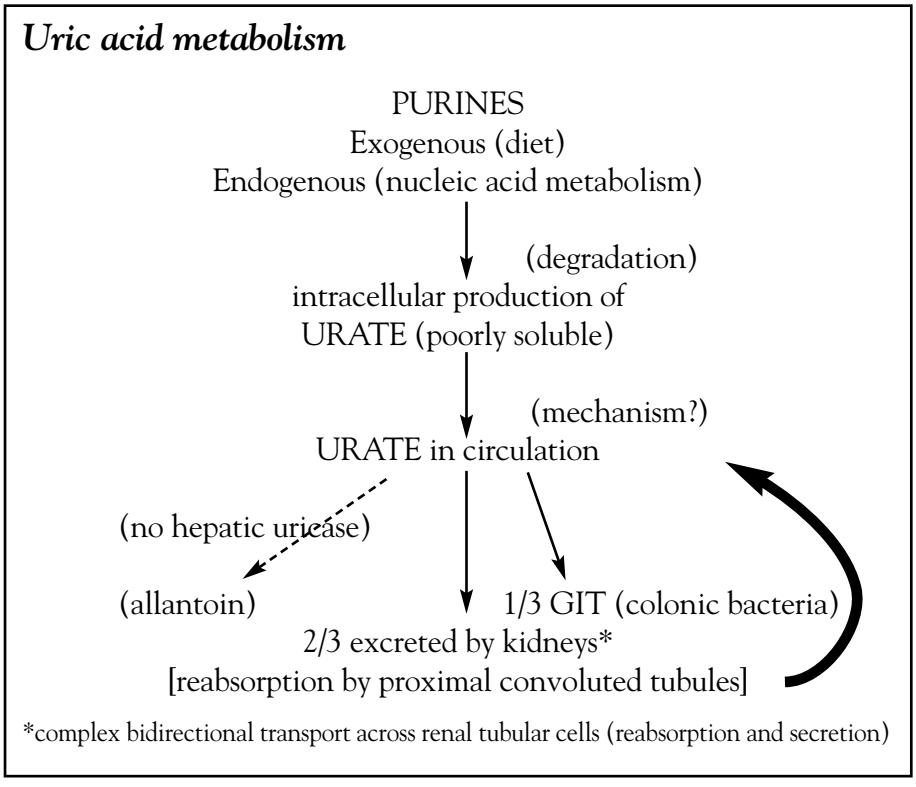

Figure 1. *Uric acid biochemistry in men.*

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gastrointestinal tract where it undergoes degradation by colonic bacteria.

Unlike man, most mammals have a low serum uric acid level (0.5 to 1.0 mg/decilitre), owing to the presence of the enzyme uricase, which converts uric acid to allantoin. There have been hypotheses concerning evolutionary advantage of the loss of urate oxidase (uricase) activity in humans. It may have occurred as a means to increase blood pressure in early hominoids in response to a low-sodium and a low-purine diet. Uric acid is an oxidant in plasma and counteraction of oxidative stress of cardiovascular disease may be a further evolutionary advantage.

Humans are the only mammals in which gout develops spontaneously as a result of the common presence of hyperuricaemia. Absolute hyperuricaemia occurs when the serum monosodium urate exceeds the limit of solubility which occurs at concentrations greater than 0.51 mmol/L. Relative hyperuricaemia occurs when serum urate exceeds the upper limit of an arbitrary normal range (usually central 95% of distribution of relevant population). In men that is 0.45 mmol/L and in women 0.35 mmol/L.

Epidemiology of hyperuricaemia and gout

Diet and alcohol have been known for centuries to be risk factors for gout. Gout was originally a disease of the affluent, "the Patrician Malady", "a disease of kings and king of disease". Now it is available for all, especially those on a "Western" diet.

Insight into the modern perspective of diet and alcohol as risk factors for gout in men has come from Hyon Choi and colleagues from Boston in three publications. Arising out of the Health Professionals Follow-up Study.[1-3] This is an ongoing longitudinal study by questionnaire involving 51,529 male dentists, optometrists, osteopaths, pharmacists, podiatrists and veterinarians who were 40 to 75 years of age in 1986. Of the 49,932 men who provided complete dietary information, 2,782 (5.6%) reported a history of gout on the baseline questionnaire. These men were excluded from the analysis, leaving 47,150 participants followed prospectively over 12 years. There were 730 confirmed new cases of gout.

In the study entitled Purine-rich foods, dairy and protein intakes, and the risk of gout in men,[1] higher levels of meat and seafood consumption were associated with increased risk of gout, whereas a higher level of consumption of dairy products was associated with a decreased risk. Moderate intake of purine rich vegetables or protein was not associated with an increased risk of gout. Each additional daily serve of meat, increased the risk of gout 21%. Each additional weekly serve of seafood increased the risk of gout 7%.

These findings were supported by a cross sectional survey of 14,809 adults which showed that higher levels of meat and seafood consumption were associated with higher serum levels of uric acid, but that total protein intake was not.[4] Daily consumption was inversely associated with the serum uric acid level.

In the publication, "Alcohol intake and risk of incident gout in men: a prospective study", Choi HK et al.[2] found that the relative risk of acquiring gout in relation to alcohol was 1.32 for 10-15 g/day and 2.53 for > 50 g/day. It was of interest that the relative risk of gout differed according to the daily serve of types of alcohol: 1.49/ for beer, 1.15/ for spirits and 1.04/ for wine.

Alcohol-induced gout occurs not only as a consequence of hyperuricaemia (particularly purine load from beer), but also there is the tendency to co-existence in heavy drinkers of trauma, and of hypothermia of the lower extremities. These latter factors may be relevant to the observations that alcoholic gouty patients tend to have lower serum urate than non-alcoholics during acute attacks of gout.

Choi and co-workers also showed prospectively in their Health Professionals Cohort Study that weight gain, adiposity, hypertension, renal failure and diuretic use were independent risk factors for gout in men.[3] In men with a BMI of 25 kg/m_ or more, 52% of the gout risk was attributable to increased weight. Weight appears to be a causal factor for gout in that weight gain increased the risk and reduction reduced in the risk.

Hyperuricaemia can begin in children and adolescents. Denzer C *et al.* published a study in 2003 involving 269 children with BMI greater than the 90th percentile. Positive correlations with uric acid (stepwise regression adjusted for age and sex) were: testosterone, BMI, systolic blood pressure, triglycerides and cholesterol/HDL ratio. Uric acid was considered to be a reliable indicator for the "pre-metabolic syndrome" in obese youths.

Other epidemiological studies have shown the following conditions associated with (co-morbidities) hyperuricaemia and/gout: race (eg Afro-Americans, Polynesians), ageing, obesity (primarily truncal), glucose intolerance (insulin resistance), dyslipidaemia (hypertriglyceridaemia, low HDL level), hypertension, coronary atherosclerotic heart disease, alcohol, renal insufficiency, lead intoxication, diuretics and other drugs and eclampsia.

Medications which reduce the excretion of uric acid include: thiazide diuretics, loop diuretics, low dose salicylates, cyclosporine, niacin, ethambutol, pyrazinamide and didanosine.

The link between insulin resistance and hyperuricaemia and gout has been recognised increasingly as an important issue in recent years. Additional to the correlations and co-morbidities of the insulin resistance (metabolic) syndrome, more specific mechanisms have been identified which link insulin resistance, gout and uric acid nephrolithiasis. There is evidence that insulin may mediate uric acid undersecretion due to its tubular sodium retaining effect in essential hypertensive patients. Thus insulin hypersecretion in obese subjects and those with the metabolic syndrome may mediate the hyperuricaemia. Insulin resistance lowers urinary ammonium and pH resulting in increased risk of uric acid precipitation in the collecting system despite normouricosuria.

Uric acid in hypertension and cardiovascular and renal disease

Hyperuricaemia was first associated with hypertension and cardiovascular disease in 1879. Uric acid is increased (univariately) in groups at cardiovascular risk: men, postmenopausal women, those with chronic renal disease, people with obesity and the metabolic syndrome, those who drink more alcohol, patients with hypertension and those who are on diuretics.

However, does hyperuricaemia have an independent association with, hypertension, renal disease, cardiovascular events, stroke, and progression of chronic heart failure after controlling for the other associations in multivariate analyses? The vital question which follows is whether uric acid as an independent risk factor (potential predictor) has a truly pathogenetic or causal influence on cardiovascular and renal conditions.

A comprehensive analysis of the risk factor status of hyperuricaemia in cardiovascular disease was presented by Johnson RJ *et al*:[5]

- Three studies showed that hyperuricaemia was an independent risk factor for the development of hypertension. Hyperuricaemia is also present in 25% of hypertensive patients, in 40-50% on anti-hypertensive therapy, and in up to 70% with renal insufficiency. Hyperuricaemia is associated with increased morbidity in hypertensive patients and predicts increased mortality in women and the elderly with hypertension.
- Hyperuricaemia predicts cardio-vascular events in studies of the general population.

Of 11 observational studies, all but 3 showed that the risk factor association status was independent.

- Hyperuricaemia predicts cardio-vascular events in studies in the hypertensive population. Of 7 observational studies cited, hyperuricaemia was independently associated with events in 6, while in 1 study there was only a univariate association.
- Hyperuricaemia predicts cardio-vascular events in patients with pre-existing cardiovascular disease. Three of four studies showed correlation between hyperuricaemia and events in this context, and the risk factor status was independent in two of three.

Other studies have shown that hyperuricaemia is an independent predictor of stroke in diabetic subjects, individuals with isolated systolic hypertension and the general population. Hyperuricaemia is also independently associated with a poorer outcome after stroke.

Table 1 – Independent cardiovascular and renal associations with hyperuricaemia

- *Cardiovascular events
  - – in the general population
  - – in the hypertensive population population
  - – in subjects with pre-existing CVS disease
- *Stroke in diabetic and non-diabetic subjects
- * Development of hypertension
- * Progression of chronic heart failure
- * Renal disease in the general

NB This does not apply in all studies

Hyperuricaemia (>0.58 mmol/L) is a strong, independent marker of impaired prognosis in patients with moderate to severe chronic heart failure. In chronic heart failure, hyperuricaemia is a marker of impaired oxidative metabolism, hyperinsulinaemia, inflammatory cytokine activation, increased xanthine oxidase (XO) activation. Thus the XO pathway and/or uric acid itself may be of pathophysiological importance in heart failure progression.

Hyperuricaemia has long been associated with renal disease. Approximately 20 to 60% of patients with gout have mild or moderate renal dysfunction. Before the availability of uric acid lowering agents, as many as 10 to 25% of patients with gout developed end stage renal disease. The histological lesion termed "gouty nephropathy" consists of glomerulosclerosis, interstitial fibrosis, and renal arteriosclerosis, often with focal interstitial urate crystal deposition. Such histological findings had been observed in autopsies in 79 to 99% of patients with gout. Despite the association of gout with renal disease, controversy exists as to whether soluble uric acid has an aetiological role. It had been difficult to ascribe the generalised renal injury in gout to the deposition of urate crystals for they are often only focally present. Many patients with gout have hypertension or are elderly and the renal lesions might simply reflect hypertensive or age-associated renal damage. Although there is no concrete evidence yet that uric acid bears a causal or reversible relationship to progressive renal disease in humans, animal data do support the concept. The results of the studies are mixed as to whether lowering uric acid will slow renal progression in patients with gout. The inability to resolve this issue has emphasised the need for additional studies. An important co-morbidity with hyperuricaemia is the metabolic syndrome and that has been strongly associated with chronic kidney disease.

The above findings are summarized in Table 1.

Association or causation?

It is extremely important that independent risk factor status in observational studies does not establish causation. Independence is a purely statistical concept and depends on the variable included in the multivariate model. Non causal risk factors can be independent risk factors. In 1999 Dobson[6] applied the Bradford Hill criteria for causation to the question as to whether raised serum uric acid is a cause of cardiovascular disease or death. Her conclusion was that there was important multicolinearity among the risk factors. A casual influence of hyperuricaemia in cardiovascular events had not been established. Subsequently the evidence for a causal influence of hyperuricaemia on hypertension, cardiovascular and renal disease has strengthened.[7,8]

The outstanding remaining link in the chain of evidence for hyperuricaemia as a causal factor for cardiovascular and renal disease is experimental evidence in animals and humans that lowering plasma urate concentration improves outcomes. In this context there is early evidence that control of hyperuricaemia by allopurinol in adolescents with hypertension reduces blood pressure.[11] A compelling rationale for randomized controlled studies of hyperuricaemia control, initially mainly in early hypertension, has been established. The postoperative use of allopurinol was associated with decreased mortality compared with placebo following coronary artery bypass surgery. Two

placebo controlled trials have shown that allopurinol improved endothelial function and peripheral blood flow in chronic heart failure. It has been argued that this was attributable to reduction of serum uric acid rather than other actions of inhibition of xanthine oxidase. In the Losartan Intervention For Endpoint reduction in hypertension (LIFE) study, 29% of the improved cardiovascular mortality in the Losartan therapy group was attributed an independent effect on (lowering) uric acid levels.

Treatment of hyperuricaemia

How should we treat hyperuricaemic patients (without crystal complication) who are at increased risk of hypertension, renal disease, and cardiovascular events?

First and foremost the risk factors for cardiovascular and renal disease and the causes and the associations of hyperuricaemia require systematic assessment and management in the individual patient. Although the level of evidence for benefit of lifestyle changes to reduce hyperuricaemia and its consequences is not high, the recent data from Choi *et al*[1] in respect of weight reduction and the theoretical appropriateness is compelling. Lifestyle issues are covered in the next section. Urate lowering drug therapy, as with allopurinol, may also be justified in some contexts, e.g. very high urate in patients with high cardiovascular or renal risk, and in chronic heart failure. Other circumstances which may merit antihyperuricaemic treatment in asymptomatic subjects include:

- Persistent hyperuricaemia with serum urate concentrations greater than 0.77 mmol/L in men, 0.59 mmol/L in women.
- Excretion of urinary uric acid in excess of 1100mg (6.5mmol) daily, in view of the 50% risk of uric acid calculi.
- Patients at risk of extensive tumour cytolysis to prevent acute uric acid nephrolithiasis. Allopurinol and rasburicase are effective in this context.
- Post transplant hyperuricaemia in kidney and heart transplant recipients (hyperuricaemia appears to be a potential risk factor for renal allograft nephropathy and for renal dysfunction and for a decrease in patient and graft survival).

Dietary and lifestyle interventions

The American College of Rheumatology in May 2004 presented a Hotline[9] entitled Health Professional Follow-up Study on Gout: what do we now tell patients about diet and alcohol? The essence of the bottom line statements was:

- Dietary trends, increasing obesity and metabolic syndrome prevalence are contributing to the increasing prevalence of gout in the US.
- Gout patients need to pay attention to weight management, including moderation in the intake of meat and seafood rich in cholesterol and saturated fatty acids and restraint in consumption of foods and drinks with non-complex carbohydrates. High fat intake and ketosis factoring into current, popular "low-carb" diets have a variety of health risks including possible worsening of gout. Exercise should also be stressed.
- In the obese, controlled weight management and reduction in alcohol consumption have the potential to lower serum urate in a quantitatively similar way to relatively unpalatable "low purine" diets.
- For patients with established gout, moderation in the consumption of not only beer but also other forms of alcohol (perhaps excluding wine) is essential. Moderate beer consumption is acceptable in most patients with therapeutically well-controlled hyperuricaemia and gout.
- Non-fat milk and low-fat yoghurt have a variety of health benefits, maybe including reduced risk of gout, but dairy products have not yet been established (one controlled trial only) to have clinically meaningful antihyperuricaemic effects for patients with established gout.

Newer agents for control of hyperuricaemia

With limited options in current hyperuricaemia treatment, particularly in those intolerant to allopurinol, it is encouraging that newer agents are emerging. Febuxostat, a non-purine xanthine oxidase selective inhibitor, has been shown to be effective in reducing serum urate levels. At present, phase II and III data are available with evidence of gout flare reduction and tophi shrinkage. In contrast to allopurinol, this drug is extensively metabolised in the liver with only 5% unchanged drug in the urine and no decrease in clearance in renal insufficiency.

Only phase I results are available for Puricase (PEGylated uricase) and it appears that urate level reduction can be achieved with a single intravenous infusion. A phase II study has been in progress with the aim of evaluating efficacy and safety of Puricase via repeated infusions.

Rasburicase, a recombinant urate oxidase, is currently available and is effective in the management of malignancy-associated hyperuricaemia in paediatrics and adult patients.

In the management of co-morbid patients with hyperlipidaemia it is useful to keep in mind that losartin and fenofibrilate are uricosuric and this may influence their selection.

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ST VINCENT'S CLINIC FOUNDATION 2005 RESEARCH GRANT RECIPIENTS

The Ladies Committee Sister Mary Bernice Grant – $100,000
Dr Diane Fatkin: "Identification of disease genes in familial atrial fibrillation"

K&A Collins Cancer Research Grant – $50,000
Dr Bryce Vissel: "Role of glutamate in regulating cell proliferation in the central nervous system"

Tancred Trust Research Grant – $50,000
Dr Janet Rimmer: "Identifying novel pathogenic mechanisms in nasal polyposis, asthma and aspirin intolerance"

Di Boyd Cancer Grant – $20,000
Dr Yi-Mo Deng: "Single nucleotide polymorphism-based real time PCR method for haematopoietic chimerism assay post allogenic stem cell transplantation"

Froulop Research Grant – $20.000
Professor Reginald Lord: "Phenotyping of vascular dendritic cells in atherosclerotic plaques (with special attention in rupture-prone regions)"

Annual Grants – $20,000 each
- A/Prof Ron Grunstein: "Forced oscillation technique to measure upper airway function in sleep apnoea"
- Dr Helen Tao: "Generation of intervertebral disc cells from human adult bone marrow mesenchymal stem cells"
- Dr Stephanie Wilson: "Modulation of insulin resistance and its effects on cardiovascular function and inflammation in overweight patients with acute coronary syndromes: a prospective study"
- Professor Bruce Brew: "Kynurenine pathway in the pathogenesis of amytrophic lateral sclerosis"

Travelling Scholarship – $10,000
Dr Jerry Greenfield: Postdoctoral research project at Addenbrook's Hospital in Cambridge: "Detailed phenotypic characterisation of human melanocortin 4 receptor (MC4R) deficiency and other monogenic causes of severe obesity"